



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 487/04, 491/06, A61K 31/47</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/49709</b> <b>(43) International Publication Date:</b> 31 December 1997 (31.12.97)
<b>(21) International Application Number:</b> PCT/US97/11222 <b>(22) International Filing Date:</b> 26 June 1997 (26.06.97)  <b>(30) Priority Data:</b> 60/021,997                      27 June 1996 (27.06.96)                      US  <b>(71) Applicant:</b> LIGAND PHARMACEUTICALS INCORPORATED [US/US]; 9393 Towne Centre Drive, San Diego, CA 92121 (US).  <b>(71)(72) Applicants and Inventors:</b> EDWARDS, James, P. [US/US]; 8723 Hesby Court, San Diego, CA 92129 (US). HIGUCHI, Robert [US/US]; 434 Marview Drive, Solana Beach, CA 92075 (US). JONES, Todd [US/US]; 805 Highland Drive, Solana Beach, CA 92075 (US).  <b>(74) Agents:</b> JURGENSEN, Thomas, E. et al.; 9393 Towne Centre Drive, San Diego, CA 92121 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>  <div style="font-size: 2em; text-align: center;">AF</div>
<b>(54) Title:</b> ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS  <b>(57) Abstract</b> <p>Non-steroidal compounds which are high affinity, high selectivity modulators for androgen receptors are disclosed. Also disclosed are pharmaceutical compositions incorporating such compounds, methods for employing the disclosed compounds and compositions for treating patients requiring androgen receptor agonist, partial agonist or antagonist therapy, intermediates useful in the preparation of the compounds and processes for the preparation of the androgen receptor modulator compounds.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

**ANDROGEN RECEPTOR MODULATOR  
COMPOUNDS AND METHODS**

**Related Applications**

5           This application claims the benefit of U.S. Provisional Application No. 60/021,997, filed June 27, 1996.

**Field of the Invention**

10           This invention relates to non-steroidal compounds that are modulators (i.e. agonists and antagonists) of androgen receptors, and to methods for the making and use of such compounds.

**Background of the Invention**

15           Intracellular receptors (IRs) form a class of structurally-related genetic regulators scientists have named "ligand dependent transcription factors." R.M. Evans, 240 *Science*, 889 (1988). Steroid receptors are a recognized subset of the IRs, including the progesterone receptor (PR), androgen receptor (AR), estrogen receptor (ER), glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Regulation of a gene by such factors requires both the IR itself and a corresponding ligand which has the ability to selectively bind to the  
20   IR in a way that affects gene transcription.

          Ligands to the IRs can include low molecular weight native molecules, such as the hormones progesterone, estrogen and testosterone, as well as synthetic derivative compounds such as medroxyprogesterone acetate, diethylstilbesterol and 19-nortestosterone. These ligands, when present in the fluid surrounding a cell, pass through the outer cell  
25   membrane by passive diffusion and bind to specific IR proteins to create a ligand/receptor complex. This complex then translocates to the cell's nucleus, where it binds to a specific gene or genes present in the cell's DNA. Once bound to DNA, the complex modulates the production of the protein encoded by that gene. In this regard, a compound which binds an IR and mimics the effect of the native ligand is referred to as an "agonist", while a  
30   compound that inhibits the effect of the native ligand is called an "antagonist."

          Ligands to the steroid receptors are known to play an important role in health of both women and men. For example, the native female ligand, progesterone, as well as synthetic analogues, such as norgestrel (18-homonorethisterone) and norethisterone (17 $\alpha$ -ethinyl-19-

nortestosterone), are used in birth control formulations, typically in combination with the female hormone estrogen or synthetic estrogen analogues, as effective modulators of both PR and ER. On the other hand, antagonists to PR are potentially useful in treating chronic disorders, such as certain hormone dependent cancers of the breast, ovaries, and uterus, and  
5 in treating non-malignant conditions such as uterine fibroids and endometriosis, a leading cause of infertility in women. Similarly, AR antagonists, such as cyproterone acetate and flutamide have proved useful in the treatment of prostatic hyperplasia and cancer of the prostate.

The effectiveness of known modulators of steroid receptors is often tempered by  
10 their undesired side-effect profile, particularly during long-term administration. For example, the effectiveness of progesterone and estrogen agonists, such as norgestrel and diethylstilbesterol respectively, as female birth control agents must be weighed against the increased risk of breast cancer and heart disease to women taking such agents. Similarly, the progesterone antagonist, mifepristone (RU486), if administered for chronic indications,  
15 such as uterine fibroids, endometriosis and certain hormone-dependent cancers, could lead to homeostatic imbalances in a patient due to its inherent cross-reactivity as a GR antagonist. Accordingly, identification of compounds which have good specificity for one or more steroid receptors, but which have reduced or no cross-reactivity for other steroid or intracellular receptors, would be of significant value in the treatment of male and female  
20 hormone responsive diseases.

A group of quinoline analogs having an adjacent polynucleic ring system of the indene or fluorene series or an adjacent polynucleic heterocyclic ring system with substituents having a nonionic character have been described as photoconductive reducing agents, stabilizers, laser dyes and antioxidants. See e.g., U.S. Patent Nos. 3,798,031;  
25 3,830,647; 3,832,171; 3,928,686; 3,979,394; 4,943,502 and 5,147,844 as well as Soviet Patent No. 555,119; R.L. Atkins and D.E. Bliss, "Substituted Coumarins and Azacoumarins: Synthesis and Fluorescent Properties", 43 *J. Org. Chem.*, 1975 (1978), E.R. Bissell et al., "Synthesis and Chemistry of 7-Amino-4-(trifluoromethyl)coumarin and Its Amino Acid and Peptide Derivatives", 45 *J. Org. Chem.*, 2283 (1980) and G.N. Gromova  
30 and K.B. Piotrovskii, "Relative Volatility of Stabilizers for Polymer Materials," 43 *Khim. Prom-st.*, 97 (Moscow, 1967). Further, a group of quinoline derivatives was recently described as modulators of steroid receptors. WO 96/19458, published June 27, 1996.

### Summary of the Invention

The present invention is directed to compounds, pharmaceutical compositions, and methods for modulating processes mediated by androgen receptors (AR). More particularly, the invention relates to non-steroidal compounds and compositions which are high affinity, high specificity agonists, partial agonists (i.e., partial activators and/or tissue-specific activators) and antagonists for androgen receptors. Also provided are methods of making such compounds and pharmaceutical compositions, as well as critical intermediates used in their synthesis.

These and various other advantages and features of novelty which characterize the invention are pointed out with particularity in the claims annexed hereto and forming a part hereof. However, for a better understanding of the invention, its advantages, and objects obtained by its use, reference should be had to the accompanying drawings and descriptive matter, in which there is illustrated and described preferred embodiments of the invention.

### Definitions and Nomenclature

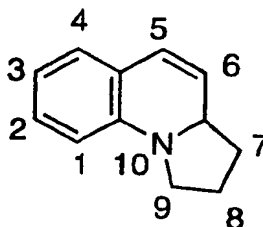
As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise. Furthermore, in an effort to maintain consistency in the naming of compounds of similar structure but differing substituents, the compounds described herein are named according to the following general guidelines. The numbering system for the location of substituents on such compounds is also provided.

The term alkyl, alkenyl, alkynyl and allyl includes straight-chain, branched-chain, cyclic, saturated and/or unsaturated structures, and combinations thereof.

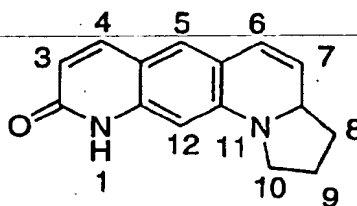
The term aryl refers to an optionally substituted six-membered aromatic ring, including polyaromatic rings and polycyclic ring systems of from two to four, more preferably two to three, and most preferably two rings.

The term heteroaryl refers to an optionally substituted five-membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of carbon, oxygen, nitrogen and sulfur, including polycyclic rings of from two to four, more preferably two to three, and most preferably two rings, or a six-membered heterocyclic ring containing one or more heteroatoms selected from the group consisting of carbon and nitrogen, including polycyclic rings of from two to four, more preferably two to three, and most preferably two rings.

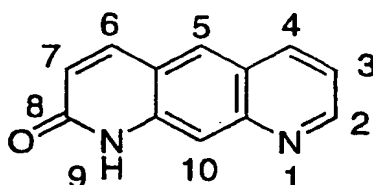
A 6a,10-dihydro-pyrrolidino[1,2a]quinoline is defined by the following structure.



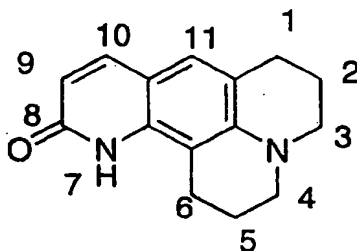
A 7a,10dihydro-2-pyridono[5,6g]pyrrolidino[1,2a]quinoline is defined by the following structure.



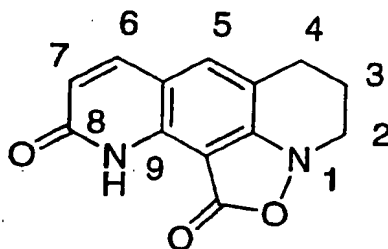
An 8-pyridono[5,6g]quinoline is defined by the following structure.



An 8-pyridono[6,5i]julolidine is defined by the following structure.



An 1,10-[1,3-dihydro-3-oxo-(2,1-isooxazolyl)]-8-pyridono[5,6g]quinoline is defined by the following structure.

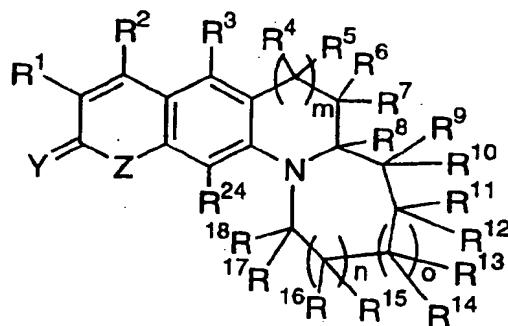


5

### Detailed Description of Embodiments of the Invention

10

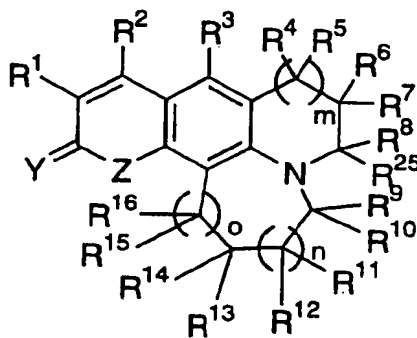
Compounds of the present invention are defined as those having the formula:



OR

(I)

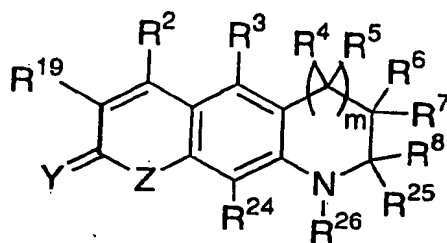
15



OR

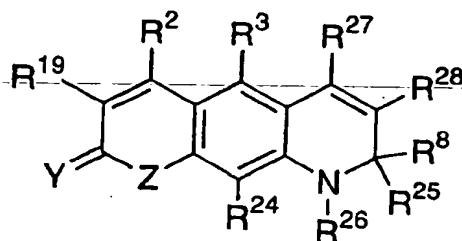
(II)

6



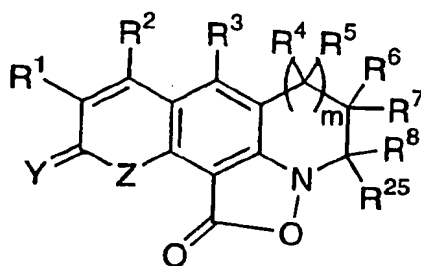
OR

(III)



OR

(IV)



wherein:

(V)

$R^1$  is hydrogen, F, Cl, Br, I,  $\text{NO}_2$ ,  $\text{OR}^{20}$ ,  $\text{NR}^{21}\text{R}^{22}$ ,  $\text{SR}^{20}$ , a  $\text{C}_1$  -  $\text{C}_4$  alkyl or perhaloalkyl, or is an optionally substituted allyl, arylmethyl, alkynyl, alkenyl, aryl or heteroaryl, where  $R^{21}$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_6$  alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl,  $\text{SO}_2\text{R}^{23}$  or  $\text{S(O)R}^{23}$ , where  $R^{23}$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_6$  alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl,  $R^{20}$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_6$  alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl, and  $R^{22}$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_4$  alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl,  $\text{OR}^{20}$  or  $\text{NHR}^{21}$ ;



$R^2$  is hydrogen, F, Br, Cl, a  $C_1 - C_4$  alkyl or perhaloalkyl, aryl, heteroaryl,  $CF_3$ ,  $CF_2H$ ,  $CFH_2$ ,  $CF_2OR^{20}$ ,  $CH_2OR^{20}$ , or  $OR^{20}$ , where  $R^{20}$  has the same definition given above;

$R^3$  is hydrogen, a  $C_1 - C_4$  alkyl, F, Cl, Br, I,  $OR^{20}$ ,  $NR^{21}R^{22}$  or  $SR^{20}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^4$  and  $R^5$  each independently are hydrogen, a  $C_1 - C_4$  alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , or  $R^4$  and  $R^5$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^6$  and  $R^7$  each independently are hydrogen, a  $C_1 - C_4$  alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , or  $R^6$  and  $R^7$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^8$  is hydrogen, a  $C_1 - C_{12}$  alkyl or perfluoroalkyl, hydroxymethyl, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl;

$R^9$  through  $R^{18}$  each independently are hydrogen, a  $C_1 - C_4$  alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , or any two of  $R^9$  through  $R^{18}$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^{19}$  is F,  $NO_2$  or  $SR^{20}$ , where  $R^{20}$  has the definition given above;

$R^{24}$  is hydrogen, a  $C_1 - C_4$  alkyl, F, Cl, Br, I,  $NO_2$ ,  $OR^{20}$ ,  $NR^{21}R^{22}$  or  $SR^{20}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^{25}$  is hydrogen, a  $C_1 - C_{12}$  alkyl, or perfluoroalkyl, hydroxymethyl, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or  $R^{25}$  and  $R^8$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

5  $R^{26}$  is hydrogen, a  $C_1 - C_6$  alkyl or perfluoroalkyl,  $NO_2$ ,  $OR^{20}$ ,  $C(O)R^{20}$ ,  $C(O)OR^{20}$ ,  $C(O)NR^{21}R^{22}$ , or an optionally substituted aryl, heteroaryl, allyl or arylmethyl, where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^{27}$  and  $R^{28}$  each independently are hydrogen, F, Cl, Br, I,  $OR^{20}$ ,  $NR^{21}R^{22}$ , a  $C_1 - C_4$  alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , or  $R^{27}$  and  $R^{28}$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$m$  is 0 or 1;

15  $n$  is 0 or 1; and

$o$  is 0 or 1;

$Y$  is O or S;

$Z$  is O, S, NH,  $NR^{22}$  or  $NCOR^{22}$ , where  $R^{22}$  has the same definition given above;

and

20 any two of  $R^4$  through  $R^8$ ,  $R^{25}$  and  $R^{28}$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above.

In a preferred aspect, the present invention provides a pharmaceutical composition comprising an effective amount of an androgen receptor modulating compound of formulae  
25 I through V shown above wherein  $R^1$  through  $R^{28}$ ,  $Y$ ,  $Z$ ,  $m$ ,  $n$  and  $o$  all have the same definitions as given above.

In a further preferred aspect, the present invention comprises a method of modulating processes mediated by androgen receptors comprising administering to a patient an effective amount of a compound of the formulae I through V shown above, wherein R<sup>1</sup> through R<sup>28</sup>, Y and Z all have the same definitions as those given above.

5 Any of the compounds of the present invention can be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, 10 pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydroxymethyl)aminomethane. Additional pharmaceutically acceptable salts are known to those skilled in the art.

AR agonist, partial agonist and antagonist compounds of the present invention will 15 prove useful in the treatment of acne, male-pattern baldness, male hormone replacement therapy, wasting diseases, hirsutism, stimulation of hematopoiesis, hypogonadism, prostatic hyperplasia, various hormone-dependent cancers, including, without limitation, prostate and breast cancer and as anabolic agents.

It will be understood by those skilled in the art that while the compounds of the 20 present invention will typically be employed as a selective agonists, partial agonists or antagonists, that there may be instances where a compound with a mixed steroid receptor profile is preferred. For example, use of a PR agonist (i.e., progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR 25 and MR modulating activity, may prove useful. Specifically, the mixed MR effects would be useful to control water balance in the body, while the AR effects would help to control any acne flare ups that occur.

Furthermore, it will be understood by those skilled in the art that the compounds of the present invention, including pharmaceutical compositions and formulations containing 30 these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, the compounds of the present invention can

be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

- 5 Representative AR modulator compounds (i.e., agonists and antagonists) according to the present invention include: (*R/S*)-6,7,7a,11-tetrahydro-7a-methyl-4-trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-a]quinoline; (*R/S*)-3-fluoro-6,7,7a,11-tetrahydro-7a-methyl-4-trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-a]quinoline; (*R/S*)-6,7,7a,11-tetrahydro-1,7a-dimethyl-4-trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-a]quinoline; (*R/S*)-3-fluoro-6,7,7a,11-tetrahydro-1,7a-dimethyl-4-trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-a]quinoline; 11-(trifluoromethyl)-9-pyridon[6,5-i]julolidine; 8-methyl-11-(trifluoromethyl)-9-pyridon[6,5-i]julolidine; 7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 6-Difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-2,2,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 6-difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-2,2,9-trimethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-1,2,2,9-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 6-difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-1,2,2,9-tetramethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2-dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 1,10-[1,3-dihydro-3-oxo-(2,1-isoxazolyl)]-1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2-dihydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-2,2,4,9,10-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-1,2,2,4,10-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 1,2,3,4-tetrahydro-1-hydroxy-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 1,2,3,4-tetrahydro-1-hydroxy-2,2,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 2,2-diethyl-7-fluoro-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; (*R/S*)-4-Ethyl-1-formyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; (*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-1-(trifluoroacetyl)-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; (*R/S*)-1-Acetyl-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; (*R/S*)-4-Ethyl-1,2,3,4-

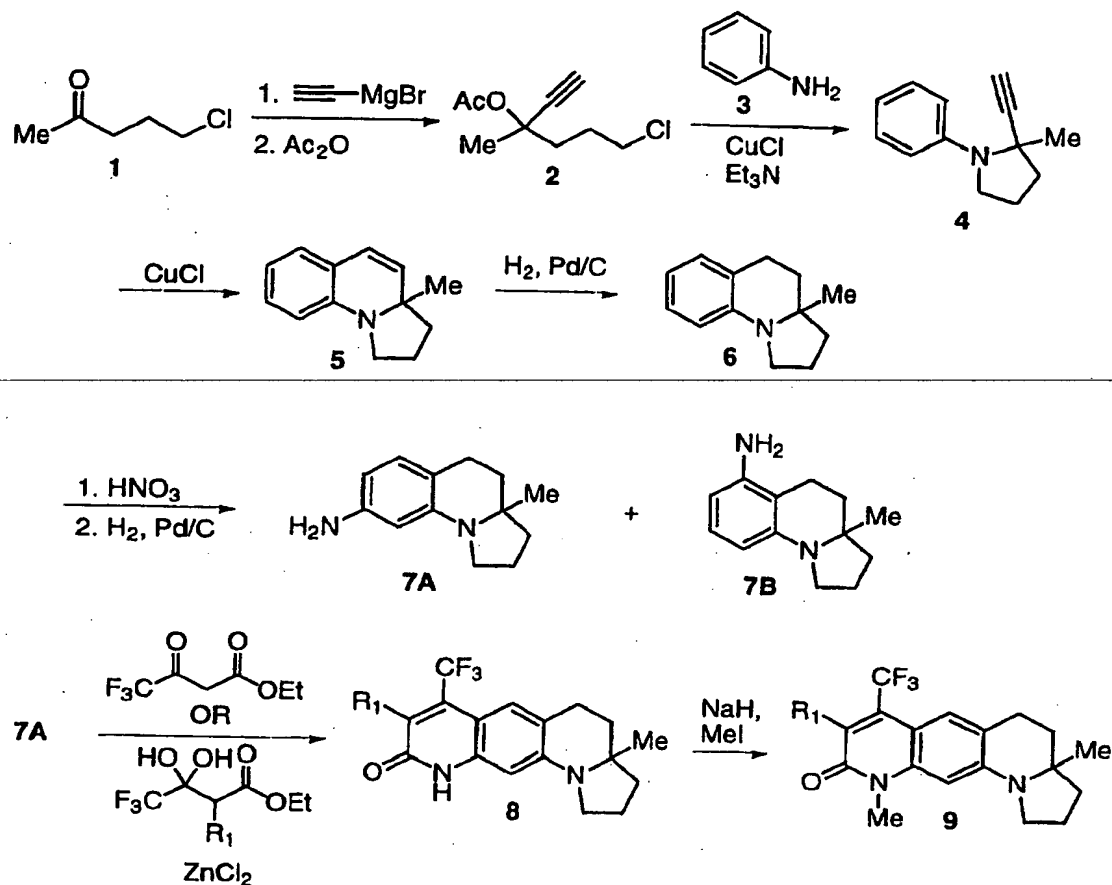
tetrahydro-10-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; 1,2,3,4-Tetrahydro-2,2-dimethyl-10-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; 1,2,3,4-Tetrahydro-2,2-dimethyl-7,10-dinitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; and (*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-1-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline.

5        Compounds of the present invention, comprising classes of heterocyclic nitrogen compounds and their derivatives, that can be obtained by routine chemical synthesis by those skilled in the art, e.g., by modification of the heterocyclic nitrogen compounds disclosed or by a total synthesis approach.

10        The sequence of steps for several general schemes to synthesize the compounds of the present invention are shown below. In each of the Schemes the R groups (e.g.,  $R^1$ ,  $R^2$ , etc.) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulas I through V also comprise potential substituents for the analogous positions on the structures within the Schemes.

15

Scheme I

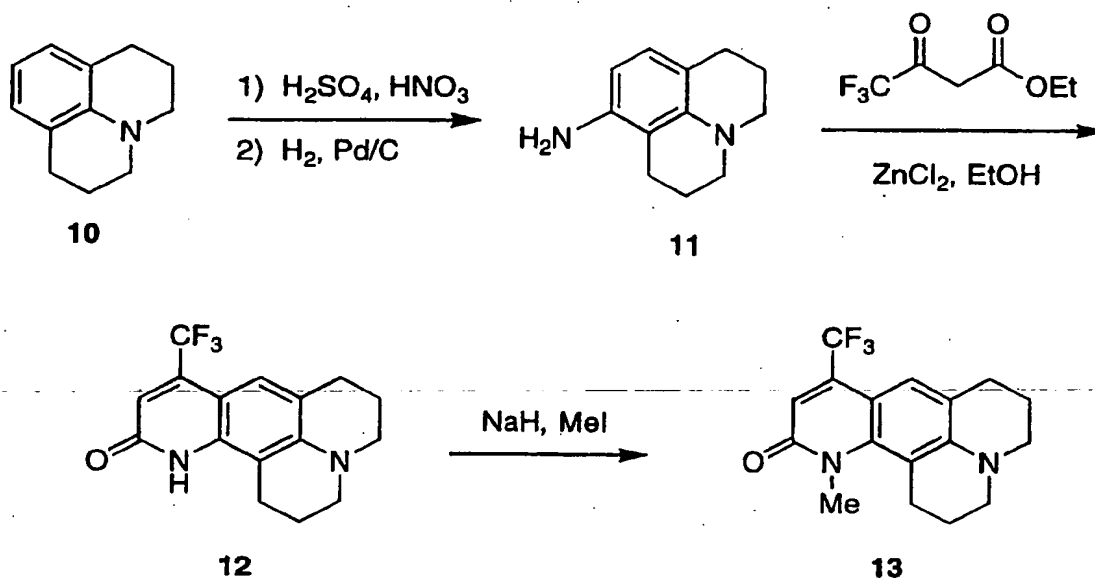


- 5 The process of Scheme I begins with an acetylide addition to 5-chloro-2-pentanone (Compound 1) with, for example, ethynylmagnesium bromide. The alcohol is then esterified to the corresponding acetate (Compound 2) with, for example, acetic anhydride and 4-dimethylaminopyridine in pyridine. A tandem propargylation/alkylation of Compound 2 with aniline (Compound 3) in the presence of a copper (I) or copper (II) salt, such as copper(I) chloride, and a base, such as triethylamine, affords Compound 4. See Y. Imada, M. Yuasa, I. Nakamura and S.-I. Murahashi, "Copper(I)-Catalyzed Amination of Propargyl Esters. Selective Synthesis of Propargylamines, 1-Alken-3-ylamines, and (Z)-Allylamines.", *J. Org. Chem.* **1994**, *59*, 2282, the disclosure of which is herein incorporated by reference. Cyclization of Compound 4 occurs in the presence of a copper catalyst, such as copper(I) chloride, to afford Compound 5. See N. R. Easton and D. R. Cassady, "A
- 10
- 15

Novel Synthesis of Quinolines and Dihydroquinolines." *J. Org. Chem.* **1962**, 27, 4713, and N. R. Easton and G. F. Hennion, "Metal Catalyst Process for Converting  $\alpha$ -Amino-Acetylenes to Dihydroquinoline", U. S. Patent 3,331,846 (1967), the disclosure of which is herein incorporated by reference.

- 5        Reduction of the olefin with, for example, hydrogen over a metal catalyst such as palladium on carbon, affords Compound 6. Nitration of Compound 6 with, for example, fuming nitric acid, followed by reduction of the nitro group with, for example, hydrogen over a metal catalyst such as palladium on carbon, affords the desired diamine (Compound 7A) along with small amounts of a regioisomer, which was separated (Compound 7B). A
- 
- 10    Knorr cyclization of Compound 7A with a  $\beta$ -keto ester or hydrated derivative, effected by, for example, zinc chloride, affords a compound of structure 8. See: E. T. McBee, O. R. Pierce, H. W. Kilbourne, and E. R. Wilson, "The Preparation and Reactions of Fluorine-containing Acetoacetic Esters." *J. Am. Chem. Soc.* **1953**, 75, 3152, the disclosure of which is herein incorporated by reference, for the preparation of the fluorinated acetoacetate
- 15    reagents. A compound of structure 8 may be further transformed into a compound of structure 9 by treatment of structure 8 with a base, such as sodium hydride, and an alkylating agent, such as methyl iodide.

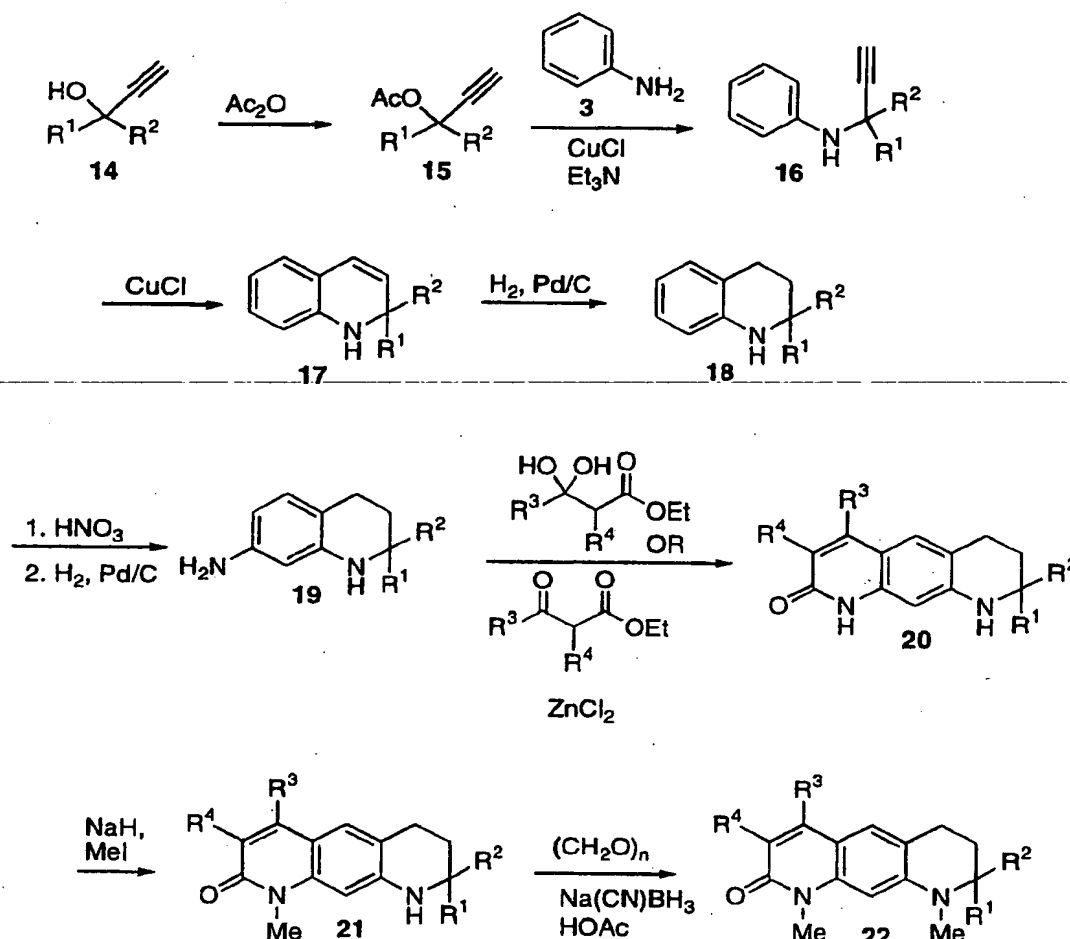
## Scheme II



The process of **Scheme II** begins with the nitration of a tricyclic tetrahydroquinoline such as julolidine, Compound **10**, followed by reduction of the nitro group to afford an aniline such as Compound **11**. Treatment of Compound **11** with a  $\beta$ -keto ester such as ethyl 4,4,4-trifluoroacetoacetate and a Lewis acid such as zinc chloride (the Knorr reaction) affords a tetracyclic quinolinone such as Compound **12**. The quinoline may be further functionalized by alkylation of the amide nitrogen by, for example, treatment with a base such as sodium hydride followed by the addition of an alkylating agent such as iodomethane, to afford a compound like Compound **13**.



## Scheme III

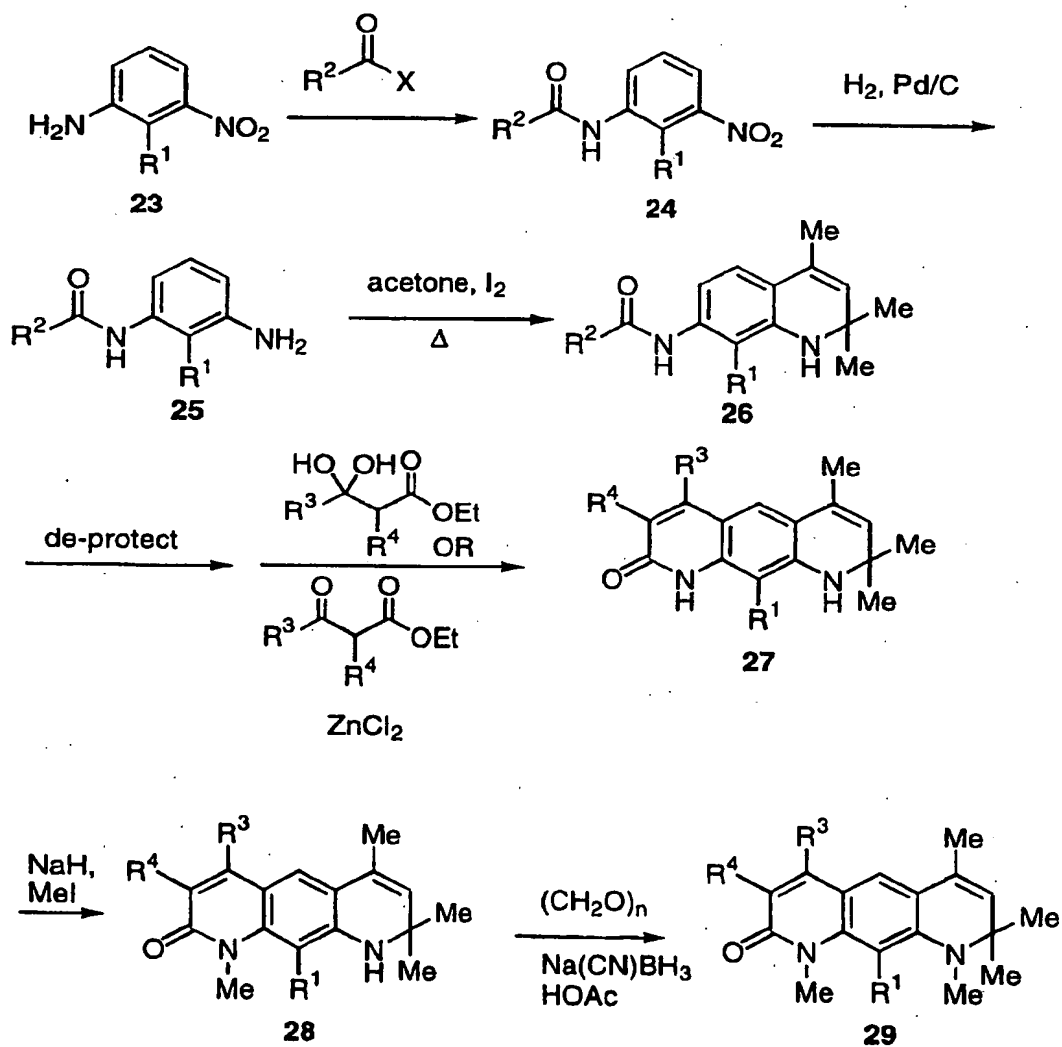


The process of **Scheme III** begins with an esterification of a propargyl alcohol (structure 14) with, for example, acetic anhydride and 4-dimethylaminopyridine in pyridine (structure 15). Alkylation of the acetate with aniline (Compound 3) in the presence of a copper(I) or copper(II) salt, such as copper(I) chloride, and a base, such as triethylamine affords a compound of structure 16. Cyclization of structure 16 occurs in the presence of a copper catalyst, such as copper(I) chloride, to afford a compound of structure 17.

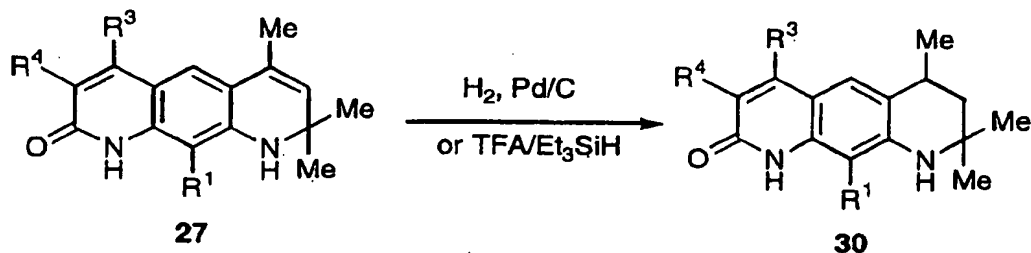
Reduction of the olefin, with for example, hydrogen over a metal catalyst, such as palladium on carbon, affords a compound of structure 18. Nitration of a compound of structure 18 with, for example, fuming nitric acid, followed by reduction of the nitro group, with, for example hydrogen over a metal catalyst such as palladium on carbon, affords a

compound of structure 19. A Knorr cyclization of a compound of structure 19 with a  $\beta$ -keto ester or hydrated derivative, effected by, for example, zinc chloride, affords a compound of structure 20. A compound of structure 20 may be further transformed into a compound of structure 21 by treatment of structure 20 with a base, such as sodium hydride, and an alkylating agent, such as methyl iodide. A compound of structure 21 may be further transformed by reductive alkylation with, for example, paraformaldehyde and sodium borohydride in acetic acid, to afford a compound of structure 22.

Scheme IV

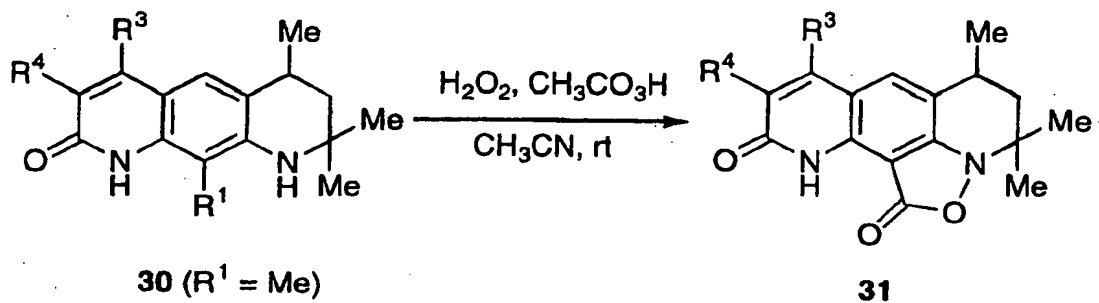


The process of **Scheme IV** begins with the acylation of a 3-nitroaniline (structure 23) with an acylating agent, for example, di-*tert*-butyl dicarbonate or trimethylacetyl chloride, to afford a compound of structure 24. Reduction of the nitro group with, for example, hydrogen over a metal catalyst such as palladium on carbon, affords the corresponding aniline (structure 25). Treatment of a compound of structure 25 with acetone and a catalyst such as iodine affords a compound of structure 26, in a process known as the Skraup cyclization. See R.H.F. Manske and M. Kulka, "The Skraup Synthesis of Quinolines", *Organic Reactions* 1953, 7, 59, the disclosure of which is herein incorporated by reference. Deprotection by either acid or base, followed by treatment of the corresponding aniline with a  $\beta$ -keto ester (or corresponding hydrate) in the presence of a Lewis acid such as zinc chloride, affords as the major product a compound of structure 27. The cyclization of an aniline as described above is known as a Knorr cyclization. See G. Jones, "Pyridines and their Benzo Derivatives: (v) Synthesis". In *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W., eds. Pergamon, New York, 1984. Vol. 2, chap. 2.08, pp 421-426. In turn, the quinolinone nitrogen may be alkylated by, for example, treatment with sodium hydride followed by iodomethane, to afford a compound of structure 28. Likewise, the quinoline nitrogen may be alkylated by, for example, treatment with paraformaldehyde and sodium cyano borohydride, to afford a compound of structure 29.

**Scheme V**

The process of **Scheme V** involves the reduction of the C(3)-C(4) olefin of a compound of structure 27 to afford a tetrahydroquinoline of structure 30, which may be accomplished by a hydrogenation with, for example, hydrogen over palladium on carbon, or by a cationic process with, for example, trifluoroacetic acid and triethylsilane.

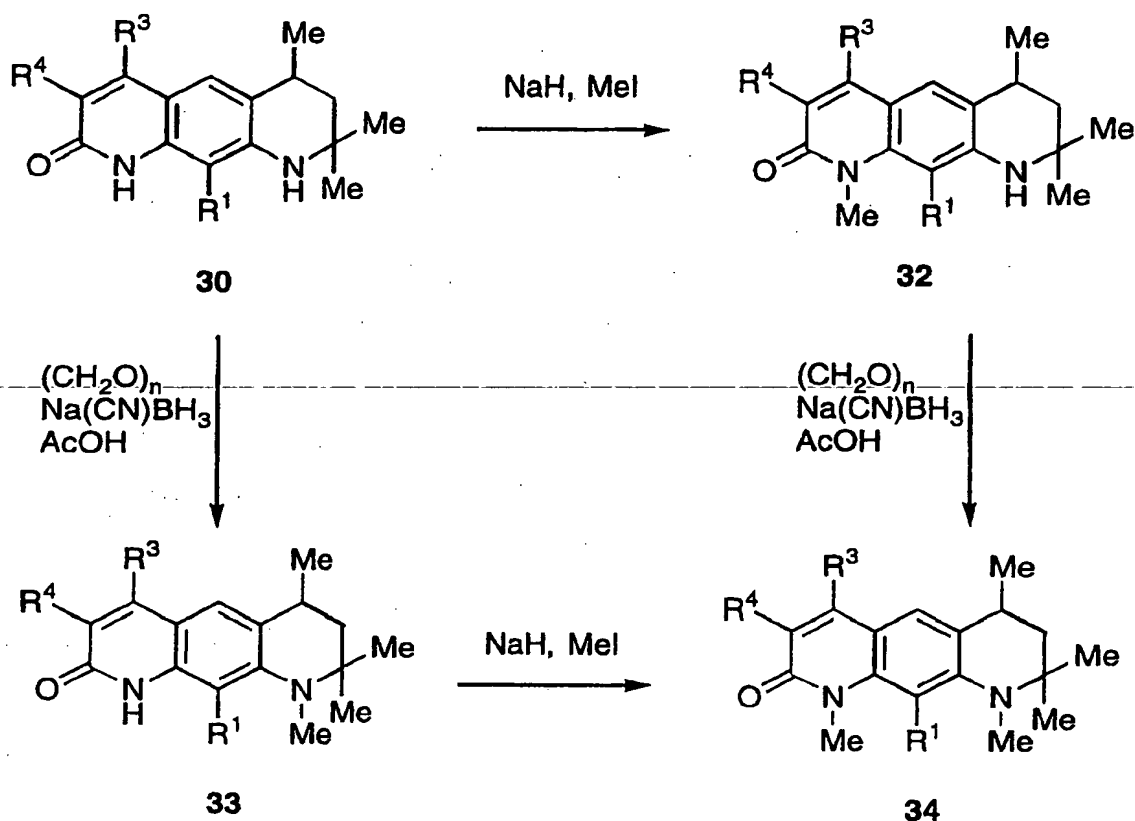
Scheme VI



- 5        The process of **Scheme VI** involves the oxidation of both the quinoline nitrogen and C(10) alkyl group of a compound of structure **30**, followed cyclization and loss of water to afford a compound of structure **31**. This may be effected by treatment of a compound of structure **30** ( $R^1 = \text{alkyl}$ , preferably methyl) with an oxygen transfer agent or combination of oxygen transfer agents, such as hydrogen peroxide in the presence of peracetic acid, to
- 10    afford a compound of structure **31**.

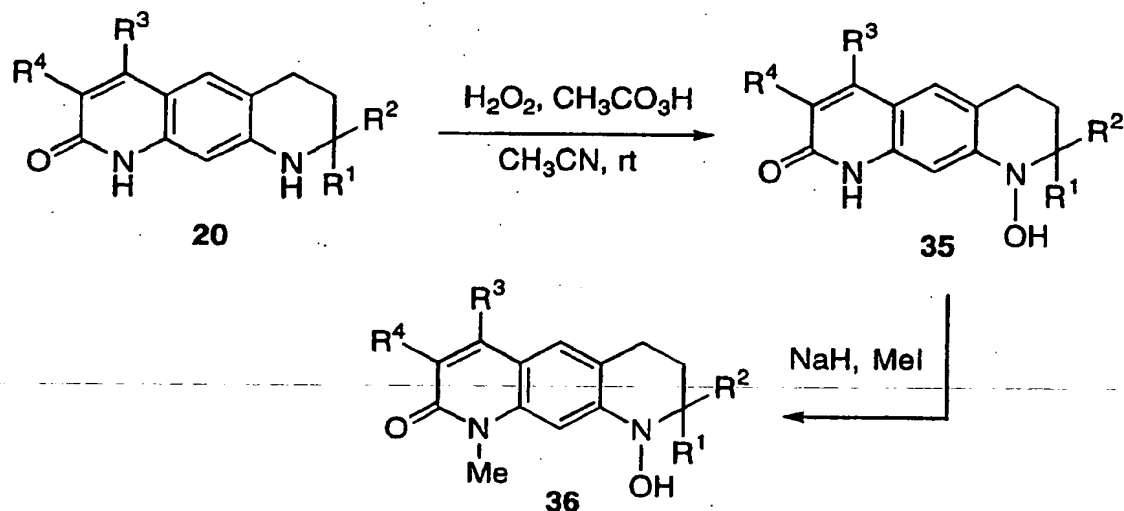
[remainder of page left blank]

Scheme VII



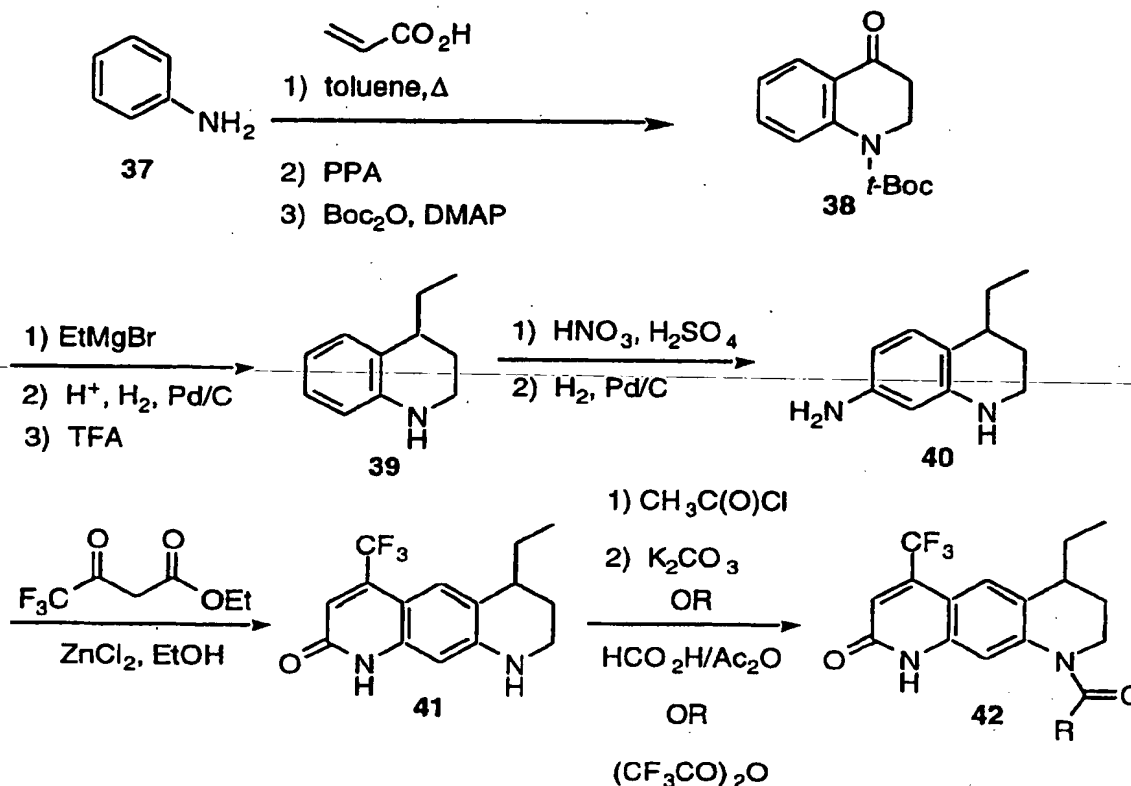
The process of Scheme VII involves the alkylation of one or both of the nitrogen atoms of a compound of structure 30. The quinolinone nitrogen may be selectively alkylated by treatment with a base, such as sodium hydride, followed by an alkylating agent, such as methyl iodide, to afford a compound of structure 32. The quinoline nitrogen may be selectively alkylated by a reductive alkylation procedure using, for example, paraformaldehyde in the presence of sodium cyano borohydride and acetic acid, to afford a compound of structure 33. Subsequently, the quinoline nitrogen of a compound of structure 32 may be reductively alkylated in a manner similar to the conversion of 30 to 33, or the quinolinone nitrogen of a compound of structure 33 may be alkylated in a manner similar to the conversion of 30 to 32. Either of these processes will afford a compound of structure 34.

## Scheme VIII



The process of **Scheme VIII** begins with the oxidation of the quinoline nitrogen atom of a compound of structure **20** with an oxygen transfer agent or mixture of oxygen transfer agents, for example, hydrogen peroxide in the presence of peracetic acid, to afford a compound of structure **35**. The quinolinone nitrogen may subsequently be alkylated by, for example, treatment with sodium hydride and methyl iodide, to afford a compound of structure **36**.

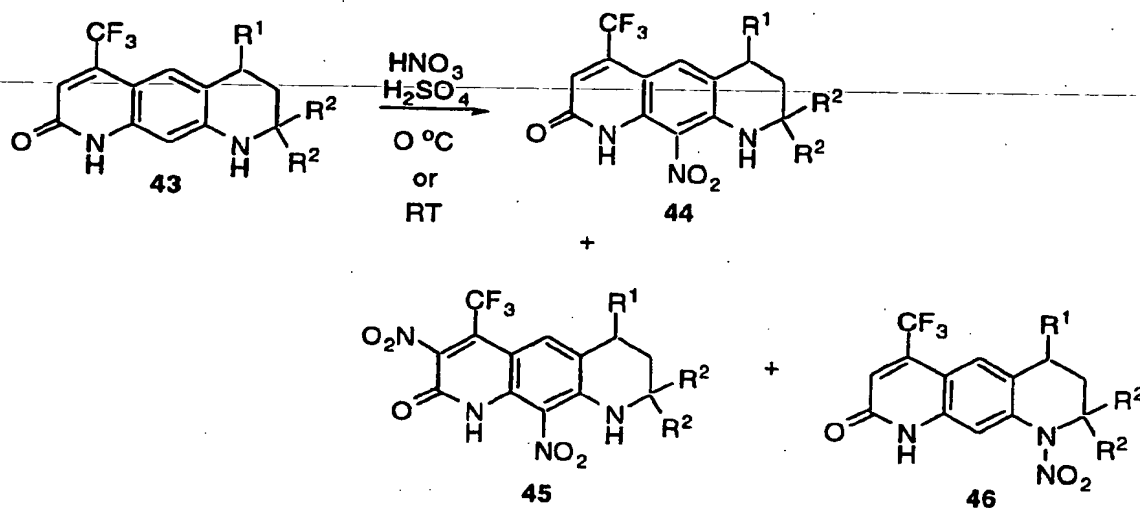
Scheme IX



- The process of Scheme IX begins with the reaction of an aniline (structure 37) with an unsaturated acid, for example acrylic acid, followed by a cyclization reaction mediated by, for example, polyphosphoric acid to afford a 4-quinolinone. The nitrogen atom is then protected by treatment with a base, for example, 4-dimethylaminopyridine, followed by the addition of an acylating agent such as di-*tert*-butyldicarbonate, to afford a compound of structure 38. Addition of an organomagnesium or organolithium reagent, with, for example, ethyl magnesium bromide, affords an alcohol. Reduction of the alcohol with, for example, hydrogen over palladium on carbon, followed by deprotection of the nitrogen atom, affords a compound of structure 39. Nitration of a compound of structure 39 by the action of nitric acid in the presence of, for example, sulfuric acid, followed by reduction of the nitro group with, for example, hydrogen over palladium on carbon, affords a 7-amino-1,2,3,4-tetrahydroquinoline of structure 40. A Knorr cyclization with a  $\beta$ -keto ester effected by, for example, zinc chloride, affords a compound of structure 41. A compound of structure 41 may be further transformed into a compounds of structure 42 by acylation of the quinoline

nitrogen, which may be accomplished in one of 2 ways. Treatment of structure **41** with an acid chloride, for example, acetyl chloride, followed by treatment with a base, for example, potassium carbonate, to afford a compound of structure **42**. Alternatively, treatment of structure **41** may be treated with an anhydride, for example, trifluoroacetic anhydride, likewise to afford a compound of structure **42**.

Scheme X



The process of Scheme X involves the treatment of structure **43** with, for example, nitric acid in the presence of, for example, sulfuric acid, to afford compounds of structure **44**, **45** and **46**.

The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, any of the steroid modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and more preferably, in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired, e.g., intravenous, oral, topical, suppository or parenteral.



In preparing the compositions in oral liquid dosage forms (e.g., suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (e.g., powders, tablets and capsules), carriers such as  
5 starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent the most advantageous oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water,  
10 although other ingredients that aid in solubility or serve as preservatives, may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment  
15 bases are petrolatum, petrolatum plus volatile silicones, lanolin, and water in oil emulsions such as Eucerin™ (Beiersdorf). Examples of suitable cream bases are Nivea™ Cream (Beiersdorf), cold cream (USP), Purpose Cream™ (Johnson & Johnson), hydrophilic ointment (USP), and Lubriderm™ (Warner-Lambert).

The pharmaceutical compositions and compounds of the present invention will  
20 generally be administered in the form of a dosage unit (e.g., tablet, capsule etc.) at from about 1 µg/kg of body weight to about 500 mg/kg of body weight, more preferably from about 10 µg/kg to about 250 mg/kg, and most preferably from about 20 µg/kg to about 100 mg/kg. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a  
25 number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

The compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of AR in a cell background or extract. They are particularly useful due to their ability to selectively activate androgen  
30 receptors, and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors.

Due to the selective specificity of the compounds of this invention for steroid receptors, these compounds can be used to purify samples of steroid receptors *in vitro*. Such purification can be carried out by mixing samples containing steroid receptors with one or more of the compounds of the present invention so that the compounds bind to the receptors of choice, and then separating out the bound ligand/receptor combination by separation techniques which are known to those of skill in the art. These techniques include column separation, filtration, centrifugation, tagging and physical separation, and antibody complexing, among others.

The compounds and pharmaceutical compositions of the present invention can advantageously be used in the treatment of the diseases and conditions described herein. In this regard, the compounds and compositions of the present invention will prove particularly useful as modulators of male sex steroid-dependent diseases and conditions such as the treatment of acne, male-pattern baldness, male hormone replacement therapy, wasting diseases, hirsutism, stimulation of hematopoiesis, hypogonadism, prostatic hyperplasia, various hormone-dependent cancers, including, without limitation, prostate and breast cancer and as anabolic agents.

The compounds and pharmaceutical compositions of the present invention possess a number of advantages over previously identified steroidal and non-steroidal compounds.

Furthermore, the compounds and pharmaceutical compositions of the present invention possess a number of advantages over previously identified steroid modulator compounds. For example, the compounds are extremely potent activators AR, preferably displaying 50% maximal activation of AR at a concentration of less than 100 nM, more preferably at a concentration of less than 50 nM, more preferably yet at a concentration of less than 20 nM, and most preferably at a concentration of 10 nM or less. Also, the selective compounds of the present invention generally do not display undesired cross-reactivity with other steroid receptors, as is seen with the compound mifepristone (RU486; Roussel Uclaf), a known PR antagonist that displays an undesirable cross reactivity on GR and AR, thereby limiting its use in long-term, chronic administration. In addition, the compounds of the present invention, as small organic molecules, are easier to synthesize, provide greater stability and can be more easily administered in oral dosage forms than other known steroidal compounds.

The invention will be further illustrated by reference to the following non-limiting Examples.

**EXAMPLE 1**

(R/S)-6,7,7a,11-Tetrahydro-7a-methyl-4-trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-a]quinoline (Compound 101, Structure 8 of Scheme 1, where R<sup>1</sup> = H)

(R/S)-6-Chloro-3-methylhex-1-yn-3-yl acetate (Compound 2)

- 5 In a 1-L, 3-neck r.b. flask with an addition funnel, a solution 5-chloro-2-pentanone (33.1 g, 274 mmol) in THF (140 mL) was treated with ethynylmagnesium bromide (564 mL of a 0.5 M solution in THF, 282 mmol, 1.03 equiv) over 0.5 h at -78 °C. The internal temperature rose to -30 °C during the addition. The mixture was allowed to warm to 0 °C and stirred for 1 h, then was poured into a cold mixture of ether (400 mL) and 1 N NaHSO<sub>4</sub>
- 10 (400 mL). The aqueous layer was extracted with ether (2 x 200 mL), and the combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) filtered, and concentrated to 42 g of a brown oil. This material was transferred to a 250-mL r.b. flask, whereupon pyridine (27 mL) and acetic anhydride (36.4 g, 356 mmol, 1.3 equiv) were added, then the flask was cooled to 0 °C. DMAP (1.67 g, 13.7 mmol, 5%) was added, and the solution was stirred for
- 15 2 d, then treated with MeOH (10 mL). After 1 h, the solution was poured into a cold mixture of ether (250 mL) and 2 N NaHSO<sub>4</sub> (250 mL). The aqueous layer was extracted with ether (250 mL), and the combined organic layers were washed with brine (250 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to a brown oil. Distillation afforded 30.5 g (58.8%) of Compound 2, a colorless oil, bp 79-80 °C @ 10 mm Hg. Data for Compound 2:
- 20 <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 3.52-3.65 (m, 2 H), 2.57 (s, 1 H), 1.85-2.15 (m, 4 H), 2.04 (s, 3 H), 1.71 (s, 3 H).

(R/S)-2-Ethynyl-2-methyl-1-phenylpyrrolidine (Compound 4)

- In a 250-mL 3-neck r.b. flask with a water cooled reflux condensor, a mixture of aniline (5.43 g, 58.3 mmol, 1.07 equiv), copper(I) chloride (0.528 g, 5.33 mmol, 0.098
- 25 equiv), and triethylamine (5.90 g, 58.3 mmol, 1.07 equiv) in THF (110 mL) was treated with 6-chloro-3-methylhex-1-yn-3-yl acetate (10.2 g, 54.3 mmol) in THF (10 mL) over 5 min. The mixture was heated at reflux for 5 h, cooled to rt, and poured into a mixture of EtOAc (100 mL) and saturated NH<sub>4</sub>Cl (100 mL). The aqueous layer was extracted with EtOAc (100 mL). The extracts were washed with brine (100 mL), dried (MgSO<sub>4</sub>), filtered, and
- 30 concentrated to a brown oil. Purification by flash chromatography (7 x 20 cm column, hexane:EtOAc, 19:1) afforded 6.35 g (63%) of compound 4 as a light golden oil. Data for

Compound 4:  $R_f$  0.32 (19:1 hexanes:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.20-7.28 (m, 2 H), 6.95 (d  $J = 8.1$ , 2 H), 6.72 (t,  $J = 7.2$ , 1 H), 3.43-3.52 (m, 1 H), 3.35-3.43 (m, 1 H), 2.40-2.50 (m, 1 H), 2.40 (s, 1 H), 2.05-2.17 (m, 2 H), 1.92-2.02 (m, 1 H), 1.62 (s, 3 H).

(*R/S*)-6*a*,10-Dihydro-6*a*-methyl-pyrrolidino[1,2-*a*]quinoline (Compound 5)

5 In a 100-mL r.b. flask equipped with a water cooled condensor, a mixture of Compound 4 (1.85 g, 10.0 mmol) and copper(I) chloride in THF (40 mL) was heated at reflux for 10 h, cooled to rt, then poured into a mixture of EtOAc (75 mL) and saturated  $\text{NH}_4\text{Cl}$  (75 mL). The aqueous layer was extracted with EtOAc (75 mL). The extracts were washed with brine (75 mL), dried ( $\text{MgSO}_4$ ), filtered, and concentrated to a brown oil.

10 Purification by flash chromatography (5 x 15 cm column, hexane:EtOAc, 24:1) afforded 1.37 g (74%) of Compound 5 as a light amber oil. Data for Compound 5:  $R_f$  0.37 (24:1 hexanes:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.06 (td,  $J = 7.9$ , 1.0, 1 H), 6.92 (dd,  $J = 7.3$ , 0.9, 1 H), 6.55 (t,  $J = 7.3$ , 1 H), 6.37 (d,  $J = 8.0$ , 1 H), 6.27 (d,  $J = 9.6$ , 1 H), 5.62 (d,  $J = 9.6$ , 1 H), 3.40-3.50 (m, 1 H), 3.28-3.38 (m, 1 H), 1.85-2.05 (m, 4 H), 1.08 (s, 3 H).

15 5,6,6*a*,10-Tetrahydro-6*a*-methyl-pyrrolidino[1,2-*a*]quinoline (Compound 6)

In a 100 mL r.b. flask, a mixture of Compound 5 (1.37 g, 7.39 mmol) and 10% Pd/C (68 mg, 5%) in EtOAc (15 mL) was flushed with hydrogen gas, then placed under a balloon of hydrogen. After 4 d, the mixture was filtered through Celite and concentrated to 1.36 g (98.6%) of Compound 6 as a colorless oil. Data for Compound 6:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.07 (t,  $J = 7.7$ , 1 H), 7.03 (d,  $J = 7.4$ , 1 H), 6.55 (td,  $J = 7.3$ , 0.9, 1 H), 6.41 (d,  $J = 8.0$  Hz, 1 H), 3.46 (td,  $J = 9.1$ , 2.1, 1 H), 3.19 (q,  $J = 9.1$  Hz, 1 H), 2.86-2.96 (m, 1 H), 2.72 (ddd,  $J = 16.5$ , 5.1, 1.9), 2.05-2.20 (m, 1 H), 1.88-2.08 (m, 3 H), 1.60 (td,  $J = 12.0$ , 7.8, 1 H), 1.42 (td,  $J = 13.2$ , 5.1, 1 H), 1.04 (s, 3 H).

(*R/S*)-5,6,6*a*,10-Tetrahydro-6*a*-methyl-2-nitropyrrolidino[1,2-*a*]quinoline

25 In a 25 mL r.b. flask, a solution of Compound 6 (1.21 g, 6.47 mmol) in concentrated sulfuric acid (12.9 mL) was cooled to  $-5^\circ\text{C}$  and treated with fuming nitric acid (0.26 mL, 6.5 mmol) dropwise over 3 min. The reddish solution was stirred for 20 min, then poured carefully into a cold mixture of  $\text{CH}_2\text{Cl}_2$  (100 mL) and saturated  $\text{K}_2\text{CO}_3$  (100 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 100 mL), and the combined organic layers  
30 were washed with phosphate buffer (pH 7, 100 mL), dried ( $\text{MgSO}_4$ ), filtered, and concentrated to an orange oil. Purification by flash chromatography (5 x 12 cm column, hexane:EtOAc, 9:1) afforded 1.11 g (74%) of (*R/S*)-5,6,6*a*,10-tetrahydro-6*a*-methyl-2-nitro-

pyrrolidino[1,2-*a*]quinoline as an orange oil. Data for (*R/S*)-5,6,6*a*,10-tetrahydro-6*a*-methyl-2-nitro-pyrrolidino[1,2-*a*]quinoline: *R*<sub>f</sub> 0.39 (9:1 hexanes:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.38 (dd, 8.1, 2.3, 1 H), 7.18 (d, *J* = 2.3, 1 H), 7.09 (d, *J* = 8.1, 1 H), 3.52 (td, *J* = 9.2, 1.9, 1 H), 3.25 (q, *J* = 9.2, 1 H), 2.88-2.98 (m, 1 H), 2.78-2.88 (m, 1 H), 2.15-2.25 (m, 1 H), 1.95-2.15 (m, 3 H), 1.64 (td, *J* = 12.1, 7.8, 1 H), 1.41 (td, *J* = 13.2, 5.2, 1 H), 1.07 (s, 3 H).

(*R/S*)-2-Amino-5,6,6*a*,10-Tetrahydro-6*a*-methyl-pyrrolidino[1,2-*a*]quinoline  
(Compound 7)

In a 25 mL r.b. flask, a mixture of (*R/S*)-5,6,6*a*,10-tetrahydro-6*a*-methyl-2-nitro-pyrrolidino[1,2-*a*]quinoline (1.02 g, 4.37 mmol) and 10% Pd/C (51 mg, 5%) in EtOAc (2.2 mL) and EtOH (2.2 mL) was flushed with hydrogen gas, then placed under an atmosphere of hydrogen. After 16 h, the mixture was filtered through Celite and concentrated to a colorless oil. Purification by flash chromatography (5 x 12 cm column, hexane:EtOAc, 7:3) afforded 589 mg (67%) of desired Compound 7A, a colorless oil. Also isolated was 89 mg (10%) of regioisomeric Compound 7B, a colorless oil. Data for Compound 7A: *R*<sub>f</sub> 0.34 (7:3 hexanes:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 6.81 (d, *J* = 7.7, 1 H), 5.95 (dd, *J* = 7.7, 2.2, 1 H), 5.79 (d, *J* = 2.1, 1 H), 3.46 (broad s, 2 H), 3.40 (td, *J* = 9.1, 1.7, 1 H), 3.16 (q, *J* = 8.9, 1 H), 2.75-2.85 (m, 1 H), 2.62 (dd, *J* = 16.1, 3.8, 1 H), 2.06-2.18 (m, 1 H), 1.85-2.05 (m, 3 H), 1.57 (td, *J* = 12.0, 7.9, 1 H), 1.39 (td, *J* = 13.0, 5.1, 1 H), 1.02 (s, 3 H). Data for Compound 7B: *R*<sub>f</sub> 0.45 (7:3 hexanes:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.91 (t, *J* = 7.9, 1 H), 6.04 (d, *J* = 7.8, 1 H), 5.96 (d, *J* = 8.1, 1 H), 3.50 (broad s, 2 H), 3.40 (td, *J* = 9.0, 2.2, 1 H), 3.23 (q, *J* = 8.7, 2 H), 2.4-2.6 (m, 2 H), 1.75-2.15 (m, 4 H), 1.55-1.65 (m, 1 H), 1.45 (td, *J* = 12.5, 6.7, 1 H), 1.00 (s, 3 H).

(*R/S*)-6,7,7*a*,11-Tetrahydro-7*a*-methyl-4-trifluoromethyl-2-pyridono[5,6-*g*]pyrrolidino[1,2-*a*]quinoline (Compound 101, Structure 8 of Scheme 1, where R<sup>1</sup> = H)

In a 100 mL r.b. flask, a suspension of Compound 7 (512 mg, 2.56 mmol), ethyl 4,4,4-trifluoroacetoacetate (518 mg, 2.82 mmol, 1.1 equiv) and 4 angstrom molecular sieves (260 mgs, 50%) in benzene (25.6 mL) was treated with ZnCl<sub>2</sub> (523 mg, 3.83 mmol, 1.5 equiv). The mixture was heated at reflux for 1 h, then treated with benzene (15 mL) and isopropanol (5 mL) to disperse the precipitates, and heated at reflux for 3 h. The mixture was treated with *p*-TsOH (190 mg, 1.00 mmol, 0.39 equiv), heated at reflux for 2 h, cooled to 0°C, and poured into a mixture of EtOAc (200 mL) and water (200 mL). The sieves were

filtered, and the organic layer was washed with brine (100 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to light brown solid. Purification by flash chromatography (5 x 12 cm column, CH<sub>2</sub>Cl<sub>2</sub>:EtOAc, 3:2) afforded 130 mg (16%) of Compound **101** as a yellow solid, plus 320 mg (39%) of impure Compound **101**. Data for Compound **14**: R<sub>f</sub> 0.15 1:1:1

- 5 EtOAc:CH<sub>2</sub>Cl<sub>2</sub>:hexanes); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) 10.54 (s, 1 H), 7.34 (s, 1 H), 6.42 (s, 1 H), 6.36 (s, 1 H), 3.52 (t, *J* = 9.7, 1 H), 3.28 (q, *J* = 9.6, 1 H), 2.92-3.05 (m, 1 H), 2.80-2.90 (m, 1 H), 2.18-2.30 (m, 1 H), 2.00-2.20 (m, 3 H), 1.68 (td, *J* = 12.1, 7.9, 1 H), 1.46 (td, *J* = 13.3, 5.1, 1 H), 1.14 (s, 3 H).

10

### EXAMPLE 2

(*R/S*)-3-Fluoro-6,7,7*a*,11-tetrahydro-7*a*-methyl-4-trifluoromethyl-2-pyridono[5,6-*g*]pyrrolidino[1,2-*a*]quinoline (Compound **102**, Structure **8** of Scheme 1, where R<sup>1</sup> = F)

#### Ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate (Scheme 1)

- In a 100 mL-r.b flask, a suspension of ethyl trifluoroacetate (31.6 g, 223 mmol, 1.44 equiv) and NaH (7.79 g of a 60% mineral oil suspension, 195 mmol, 1.05 equiv, rinsed with 20 mL of pentane) was treated with ethyl fluoroacetate (16.4 g, 154 mmol) at 50 °C over 6 h. The addition was stopped when the evolution of H<sub>2</sub> was no longer observed. The mixture was heated at 50°C for 2 h, allowed to stir at rt overnight, then poured into a mixture of ice (100 g), concentrated H<sub>2</sub>SO<sub>4</sub> (19.5 mL) and ether (200 mL). The aqueous layer was extracted with ether (200 mL). The combined organic layers were washed with phosphate buffer (pH 7, 50 mL), brine (50 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to a 2-phase oil. The lower layer was drawn off and distilled to afford 15.1 g of a colorless liquid, bp 30-31°C @ 15 mm Hg. The oil crystallized at 0°C to afford 5.76 g (18%) of ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate, a white solid. Data for ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 5.06 (d, *J* = 47.7, 1 H), 4.80 (broad s, 1 H), 4.40 (q, *J* = 7.2, 2 H), 4.07 (broad s, 1 H), 1.39 (t, *J* = 7.2, 3 H).
- 25

- In a 15-mL r.b. flask equipped with a water cooled condensor, a suspension of Compound **7** (122 mg, 0.609 mmol), ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate (147 mg, 0.670 mmol, 1.1 equiv) and 4 angstrom molecular sieves (120 mgs, 100%) in benzene (1.2 mL) was treated with ZnCl<sub>2</sub> (124 mg, 0.913 mmol, 1.5 equiv). The mixture was heated at reflux for 6 h, then treated with *p*-TsOH (23 mg, 0.12 mmol, 0.20 equiv) and EtOH (0.3
- 30

mL). After 2 h at reflux, the mixture was poured into a mixture of EtOAc (50 mL) and water (25 mL), filtered through Celite, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>), filtered, and concentrated to light brown solid. Purification by flash chromatography (3.5 x 15 cm column, CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 23:2) afforded 77 mg (37%) of Compound **102** as a yellow solid. Data for Compound **102**: R<sub>f</sub> 0.54 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 23:2); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 11.29 (s, 1 H), 7.41 (s, 1 H), 6.17 (s, 1 H), 3.53 (t, *J* = 9.5, 1 H), 3.30 (q, *J* = 9.2, 1 H), 2.95-3.05 (m, 1 H), 2.77-2.86 (m, 1 H), 2.15-2.25 (m, 1 H), 2.03-2.15 (m, 2 H), 2.00 (dd, *J* = 11.9, 6.8, 1 H), 1.60-1.70 (m, 1 H), 1.46 (td, *J* = 13.3, 4.9, 1 H), 1.10 (s, 3 H).

10

### EXAMPLE 3

(*R/S*)-6,7,7a,11-Tetrahydro-1,7a-dimethyl-4-trifluoromethyl-2-pyridono[5,6-*g*]pyrrolidino[1,2-*a*]quinoline (Compound **103**, Structure **9** of Scheme 1, where R<sup>1</sup> = H)

In a 25-mL r.b. flask, a mixture of Compound **101** (73 mg, 0.23 mmol) and NaH (36 mg of a 60% mineral oil dispersion, 0.91 mmol, 4 equiv) in THF (3.3 mL) was stirred for 0.5 h, then treated with iodomethane (129 mg, 0.91 mmol, 4 equiv). The mixture was quenched with phosphate buffer (pH 7, 20 mL), and aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to a yellow solid. Purification by flash chromatography (3 x 15 cm column, CH<sub>2</sub>Cl<sub>2</sub>:EtOAc:hexanes, 2:1:1) afforded 31 mg (41%) of Compound **103**, a yellow solid. Data for Compound **103**: R<sub>f</sub> 0.52 (2:1:1 CH<sub>2</sub>Cl<sub>2</sub>: EtOAc:hexanes); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.44 (s, 1 H), 6.71 (s, 1 H), 6.12 (s, 1 H), 3.67 (s, 3 H), 3.56 (t, *J* = 9.0, 1 H), 3.30 (q, *J* = 9.2, 1 H), 2.95-3.05 (m, 1 H), 2.80-2.90 (m, 1 H), 2.20-2.32 (m, 1 H), 2.08-2.20 (m, 2 H), 2.03 (dd, *J* = 11.9, 6.8, 1 H), 1.68 (td, *J* = 12.2, 7.9, 1 H), 1.48 (td, *J* = 13.3, 5.1, 1 H), 1.13 (s, 3 H).



**EXAMPLE 4**

(R/S)-3-Fluoro-6,7,7a,11-tetrahydro-1,7a-dimethyl-4-trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-a]quinoline (Compound 104, Structure 9 of Scheme 1, where R<sup>1</sup> = F)

This compound was prepared in a manner similar to that described for the  
5 preparation of Compound 103 (EXAMPLE 3) from Compound 102 (40 mg, 0.12 mmol),  
NaH (9.3 mg of a 60% mineral oil dispersion, 0.23 mmol, 2 equiv), and iodomethane (33  
mg, 0.23 mmol, 2 equiv) in THF (1.2 mL) to afford 4.8 mg (12%) of Compound 104, a  
yellow solid, after chromatography (CH<sub>2</sub>Cl<sub>2</sub>: EtOAc, 24:1). Data for Compound 104: <sup>1</sup>H  
NMR (400 MHz, CDCl<sub>3</sub>) 7.46 (s, 1 H), 6.11 (s, 1 H), 3.72 (s, 3 H), 3.54 (t, J = 8.8, 1 H),  
10 3.31 (q, J = 9.1, 1 H), 2.95-3.07 (m, 1 H), 2.80-2.88 (m, 1 H), 2.20-2.30 (m, 1 H), 2.07-2.22  
(m, 2 H), 2.03 (dd, J = 12.0, 6.8, 1 H), 1.68 (td, J = 12.2, 7.9, 1 H), 1.47 (td, J = 13.4, 5.1, 1  
H), 1.12 (s, 3 H).

**EXAMPLE 5**

15 10-(Trifluoromethyl)-8-pyridono[6,5-i]julolidine (Compound 12 of Scheme II).  
7-Nitrojulolidine

In a 250 mL r.b. flask was introduced julolidine (2.12 g, 12.2 mmol), and  
concentrated sulfuric acid (14 mL). The reaction mixture was cooled to 0°C and 90% nitric  
acid (0.55 mL, 12 mmol, 1.0 equiv) was added via syringe over a period of 10 min. The  
20 reaction mixture was stirred an additional 10 min and poured over ice (100 g). The resulting  
suspension was neutralized by the slow addition of potassium carbonate (40 g) in four equal  
portions. The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 mL) and washed with saturated  
NaHCO<sub>3</sub> (1 x 100 mL). The extracts were combined, dried (MgSO<sub>4</sub>), filtered through a pad  
of Celite, and concentrated to a yellow solid (2.68 g, 99%). Data for 7-nitrojulolidine: <sup>1</sup>H  
25 NMR (400 MHz, CDCl<sub>3</sub>) 6.99 (d, J = 8.3, 1H), 6.82 (d, J = 8.3, 1H), 3.20 (q, J = 5.7, 4H),  
2.91 (t, J = 6.5, 2H), 2.77 (t, J = 6.4, 2H), 1.94 (m, 4H).

10-(Trifluoromethyl)-8-pyridono[6,5-i]julolidine (Compound 12 of Scheme II).

In a 100 mL r.b. flask, a solution of 7-nitrojulolidine (0.44 g, 2.0 mmol) in 1:1  
EtOH:EtOAc (20 mL) was treated with 10% Pd/C (200 mg) and stirred under an atmosphere  
30 of H<sub>2</sub> for 4 h. The reaction mixture was filtered and concentrated to a reddish oil (0.37 g)  
which was dissolved in EtOH (30 mL), treated with ethyl 4,4,4-trifluoroacetoacetate (0.30

mL) and zinc chloride (0.30 g), and heated at reflux for 12 h. The reaction mixture was poured into H<sub>2</sub>O (30 mL) and extracted with EtOAc (3 x 30 mL). The extracts were washed with H<sub>2</sub>O (2 x 30 mL) and brine (1 x 30 mL), combined, dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 12:1) afforded

5 Compound 12 (0.41 g, 66%) as a yellow solid. Data for Compound 12: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 12.5 (br s, 1H), 7.16 (s, 1H), 6.50 (s, 1H), 3.40 (m, 4H), 2.99 (t, *J* = 6.2, 2H), 1.95 (m, 4H), 1.91 (m, 2H).

#### EXAMPLE 6

10 7-Methyl-10-(trifluoromethyl)-8-pyridono[6,5-*i*]julolidine (Compound 13 of Scheme II).

In a 10 mL r.b. flask, a solution of Compound 12 (32 mg, 0.10 mmol) in DMF (1 mL) was treated with 60% NaH (6 mg, 0.1 mmol, 1 equiv) and treated with MeI (7 mL, 0.1 mmol, 1 equiv). The reaction mixture was stirred at rt for 6 h, poured into H<sub>2</sub>O (5 mL) and extracted with EtOAc (3 x 6 mL). The extracts were washed with H<sub>2</sub>O (1 x 5 mL) and brine

15 (1 x 6 mL), combined, dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 30:1) afforded Compound 13 (3 mg, 10%) as a yellow solid. Data for Compound 13: <sup>1</sup>H NMR (400 MHz, acetone-d<sub>6</sub>) 7.14 (s, 1H), 6.44 (s, 1H), 3.60 (s, 3H), 3.38 (m, 4H), 2.98 (t, *J* = 6.2, 2H), 1.95 (m, 4H), 1.91 (m, 2H).

20 EXAMPLE 7

7-Fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 105, Structure 20 of Scheme III, where R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = F).

2-Methyl-3-butyn-2-yl(phenyl)amine (structure 16 of Scheme III, where R<sup>1</sup> = R<sup>2</sup> =

25 Me). In a 500 mL r.b., a solution of 2-methyl-3-butyn-2-ol (10.0 mL, 0.10 mol, 1.3 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL) was treated sequentially with Et<sub>3</sub>N (15.0 mL, 0.107 mol, 1.4 equiv), acetic anhydride (11.6 mL, 0.12 mol, 1.5 equiv), and DMAP (0.61 g, 5.0 mmol, 5.0 mol%). The reaction mixture was stirred at rt for 2 h and poured into sat'd NH<sub>4</sub>Cl (60 mL). The layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 100 mL). The

30 organic layers were washed with 1 N HCl (2 x 100 mL), combined, dried (MgSO<sub>4</sub>), filtered through a pad of Celite, and the volatiles were removed by distillation (<45 °C distillate).

The residue was dissolved in THF (100 mL) and aniline (7.00 mL, 77 mmol) was added slowly via syringe, followed by CuCl (0.76 g, 10 mol%). The reaction mixture was heated to reflux for 3 h. The resulting red solution was allowed to cool to rt, the bulk of the volatiles were removed *in vacuo*, and the residue was diluted with EtOAc (120 mL). The solution was washed with sat'd NH<sub>4</sub>Cl (2 x 100 mL) and brine (1 x 100 mL). The aqueous layers were extracted with EtOAc (2 x 100 mL). The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated. Purification by silica gel chromatography (hexane:EtOAc, 16:1) afforded 10.5 g (87%) of 2-methyl-3-butyn-2-yl(phenyl)amine as a pale yellow liquid. Data for 2-methyl-3-butyn-2-yl(phenyl)amine: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.20 (t, *J* = 7.7, 2H), 6.95 (d, *J* = 7.7, 2H), 6.80 (t, *J* = 7.7, 1H), 3.65 (br s, 1H), 2.36 (s, 1H), 1.61 (s, 6H).

1,2-Dihydro-2,2-dimethylquinoline (structure 17 of Scheme III, where R<sup>1</sup> = R<sup>2</sup> = Me).

In a 1 L r.b., a solution of 2-methyl-3-butyn-2-yl(phenyl)amine (24.3 g, 152 mmol) in THF (200 mL) was treated with CuCl (1.70 g, 11 mol%) and heated at reflux for 14 h. The reaction mixture was cooled to rt, filtered, and the bulk of the THF was removed *in vacuo*. The residue was poured into sat'd NH<sub>4</sub>Cl (200 mL) and extracted with EtOAc (3 x 250 mL). The extracts were washed with sat'd NH<sub>4</sub>Cl (1 x 200 mL) and brine (1 x 200 mL), combined, dried (MgSO<sub>4</sub>), filtered through a pad of Celite, and concentrated to an orange oil. Purification by silica gel chromatography (hexane:EtOAc, 40:1) afforded 18.0 g (74%) of the quinoline as a pale yellow oil. Data for 1,2-dihydro-2,2-dimethylquinoline: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 6.95 (t, *J* = 7.7, 1H), 6.87 (d, *J* = 7.3, 1H), 6.57 (t, *J* = 7.3, 1H), 6.40 (d, *J* = 7.7, 1H), 6.25 (d, *J* = 9.7, 1H), 5.46 (d, *J* = 9.7, 1H), 3.63 (br s, 1H), 1.31 (s, 6H).

1,2,3,4-Tetrahydro-2,2-dimethylquinoline (structure 18 of Scheme III, where R<sup>1</sup> = R<sup>2</sup> = methyl).

In a 1 L r.b., a solution of the dihydroquinoline (16.2 g) in 1:1 EtOH:EtOAc (300 mL) was treated with 10% Pd/C (1.05 g) and stirred under an atmosphere of hydrogen. The reaction was monitored by <sup>1</sup>H NMR and was complete after 4 h. The reaction mixture was purged, filtered through a pad of Celite, and the pad was rinsed with EtOAc (200 mL). Concentration of the filtrate afforded 16.2 g (99%) of the tetrahydroquinoline as a pale

yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 6.98 (m, 2H), 6.60 (t,  $J = 7.3$ , 1H), 6.44 (d,  $J = 8.0$ , 1H), 2.77 (t,  $J = 6.7$ , 2H), 1.70 (t,  $J = 6.7$ , 2H), 1.21 (s, 6H).

1,2,3,4-Tetrahydro-2,2-dimethyl-7-nitroquinoline.

In a 250 mL r.b., 1,2,3,4-tetrahydro-2,2-dimethylquinoline (6.06 g) in  $\text{H}_2\text{SO}_4$  (40 mL) was cooled to  $-5^\circ\text{C}$ . To this slurry, 90%  $\text{HNO}_3$  (1.70 mL) was added dropwise over a 15 min period. The reaction mixture was stirred an additional 15 min and poured over ice (300 g).  $\text{K}_2\text{CO}_3$  (100 g) was added slowly with vigorous stirring. The residue was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 300 mL). The extracts were washed with  $\text{H}_2\text{O}$  (1 x 200 mL) and sat'd  $\text{NaHCO}_3$  (1 x 100 mL), combined, dried ( $\text{MgSO}_4$ ), filtered through pad of Celite, and concentrated. Purification by silica gel chromatography (hexane:EtOAc, 40:1 to 20:1 gradient) afforded 4.40 g (57%) of the product as an orange solid. Data for 1,2,3,4-tetrahydro-2,2-dimethyl-7-nitroquinoline:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.39 (dd,  $J = 7.9$ , 2.2, 1H), 7.27 (d,  $J = 2.2$ , 1H), 7.04 (d,  $J = 7.9$ , 1H), 3.95 (bs, 1H), 2.81 (t,  $J = 6.7$ , 2H), 1.72 (t,  $J = 6.7$ , 2H), 1.21 (s, 6H).

7-Amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline (structure 19 of Scheme III, where  $\text{R}^1 = \text{R}^2 = \text{Me}$ ).

In a 200-mL r.b. flask, a solution of 1,2,3,4-tetrahydro-2,2-dimethyl-7-nitroquinoline (1.00 g, 4.84 mmol) in 1:1 EtOH:EtOAc (40 mL) was treated with 10% Pd/C (0.20 g). The reaction mixture was de-gassed and fitted with a balloon of  $\text{H}_2$ . The reaction mixture was stirred for 6 h, de-gassed, and filtered through a pad of Celite. The pad was rinsed with EtOAc (300 mL). The filtrate was concentrated to afford 0.85 g (99%) of the crude aniline as a reddish oil. Data for 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 6.77 (d,  $J = 7.9$ , 1H), 6.00 (dd,  $J = 7.9$ , 2.2, 1H), 5.81 (d,  $J = 2.2$ , 1H), 3.47 (bs, 1H), 3.40 (bs, 2H), 2.66 (t,  $J = 6.7$ , 2H), 1.65 (t,  $J = 6.7$ , 2H), 1.18 (s, 6H).

7-Fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound 105, Structure 20 of Scheme III, where  $\text{R}^1, \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{trifluoromethyl}$ ,  $\text{R}^4 = \text{F}$ ).

This compound was prepared in a manner similar to that described for Compound 102 (EXAMPLE 2) from 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline (269 mg, 1.53 mmol), ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate (370 mg, 1.68 mmol, 1.1 equiv)

and,  $\text{ZnCl}_2$  (313 mg, 2.30 mmol, 1.5 equiv) in benzene (15 mL) followed by *p*-TsOH (72.8 mg, 0.383 mmol, 0.25 equiv) to afford 298 mg (62%) of Compound **105** after chromatography ( $\text{CH}_2\text{Cl}_2$ :EtOAc, 5:2). Data for Compound **105**:  $R_f$  0.40 (5:2  $\text{CH}_2\text{Cl}_2$ :EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 12.49 (s, 1 H), 7.39 (s, 1 H), 6.45 (s, 1 H), 4.46 (s, 1 H), 2.83 (t,  $J = 6.5$ , 2 H), 1.69 (t,  $J = 6.6$ , 2 H), 1.20 (s, 6 H); Anal. Calc'd for  $\text{C}_{15}\text{H}_{14}\text{F}_4\text{N}_2\text{O}$ : C, 57.33; H, 4.49; N, 8.91. Found: C, 57.04; H, 4.72; N, 8.74.

### EXAMPLE 8

6-Difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-8-pyridono[5,6-*g*]quinoline  
10 (Compound **106**, Structure 20 of Scheme III, where  $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{difluoromethyl}$ ,  $\text{R}^4 = \text{F}$ ).

This compound was prepared in a manner similar to that described for Compound **102** (EXAMPLE 2) from 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline (150 mg, 0.851 mmol), ethyl 2,4,4-trifluoroacetoacetate (172 mg, 0.936 mmol, 1.1 equiv), and 4 angstrom  
15 molecular sieves (75 mgs, 50%), and  $\text{ZnCl}_2$  (174 mg, 1.28 mmol, 1.5 equiv) in benzene (9.5 mL) followed by *p*-TsOH (40.5 mg, 0.213 mmol, 0.25 equiv) and EtOH (0.8 mL) to afford 116 mg (46%) of Compound **106** after chromatography ( $\text{CH}_2\text{Cl}_2$ :MeOH, 23:2) and recrystallization from EtOAc. Data for Compound **106**:  $R_f$  0.33 (23:2  $\text{CH}_2\text{Cl}_2$ :MeOH);  $^1\text{H}$   
NMR (400 MHz, acetone- $d_6$ ) 10.93 (broad s, 1 H), 7.52 (s, 1 H), 7.33 (t,  $J = 53.1$ , 1 H),  
20 6.48 (s, 1 H), 5.85 (broad s, 1 H), 2.8-2.9 (m, 2 H), 1.73 (t,  $J = 6.7$ , 2 H), 1.25 (s, 6 H).

### EXAMPLE 9

7-Fluoro-1,2,3,4-tetrahydro-2,2,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline  
(Compound **107**, Structure 21 of Scheme III, where  $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{trifluoromethyl}$ ,  $\text{R}^4 = \text{F}$ ).

This compound was prepared in a manner similar to that described for Compound **103** (EXAMPLE 3) from Compound **105** (20 mg, 0.064 mmol), NaH (3.6 mg of a 60% mineral oil dispersion, 0.088 mmol, 1.4 equiv) and iodomethane (13 mg, 0.089, 1.4 equiv) in THF (1.3 mL) to afford 11 mg (51%) of Compound **107**, a yellow solid, after  
30 chromatography ( $\text{CH}_2\text{Cl}_2$ :EtOAc, 19:1). Recrystallization from ethyl acetate afforded 5.6 mg (27%) of a yellow solid. Data for Compound **107**:  $R_f$  0.29 ( $\text{CH}_2\text{Cl}_2$ :EtOAc, 19:1);  $^1\text{H}$

NMR (400 MHz, CDCl<sub>3</sub>) 7.44 (s, 1 H), 6.32 (s, 1 H), 4.32 (broad s, 1 H), 3.66 (s, 3 H), 2.87 (t, *J* = 6.6, 2 H), 1.76 (t, *J* = 6.7, 2 H), 1.28 (s, 6 H).

#### EXAMPLE 10

5 6-Difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-2,2,9-trimethyl-8-pyridono[5,6-*g*]quinoline (Compound 108, Structure 21 of Scheme III, where R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = difluoromethyl, R<sup>4</sup> = F).

This compound was prepared in a manner similar to that described for Compound 103 (EXAMPLE 3) from Compound 106 (40 mg, 0.14 mmol), NaH (6.8 mg of a 60% mineral oil dispersion, 0.17 mmol, 1.4 equiv) and iodomethane (25 mg, 0.18, 1.4 equiv) in THF (2.6 mL) to afford 40 mg (96%) of Compound 108, a yellow solid after chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc, 19:1). Data for Compound 108: R<sub>f</sub> 0.53 (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 23:2); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) 7.57 (s, 1 H), 7.35 (t, *J* = 53.0, 1 H), 6.58 (s, 1 H), 5.87 (broad s, 1 H), 3.59 (s, 3 H), 2.87 (t, *J* = 6.6, 2 H), 1.75 (t, *J* = 6.6, 2 H), 1.27 (s, 6 H).

#### EXAMPLE 11

7-Fluoro-1,2,3,4-tetrahydro-1,2,2,9-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 109, Structure 22 of Scheme III, where R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = F).

20 In a 10-mL r.b. flask, a mixture of Compound 107 (16 mg, 0.049) and paraformaldehyde (15 mg, 0.49 mmol, 10 equiv) in AcOH (3.0 mL) was treated with sodium cyanoborohydride (15 mg, 0.24 mmol, 4.8 equiv). The resultant mixture was stirred at rt for 18h, then poured carefully into 25% aqueous NaOH (25 mL) and ice to make the mixture strongly alkaline (pH 11). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL), and the combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to a yellow solid. Purification by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>:EtOAc, 20:1) afforded 15.2 mg (91%) of Compound 109, a yellow solid. Data for Compound 109: R<sub>f</sub> 0.74 (12:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.39 (s, 1 H), 6.28 (s, 1 H), 3.74 (s, 3 H), 2.95 (s, 3 H), 2.82 (t, *J* = 6.4, 2 H), 1.85 (t, *J* = 6.4, 2 H), 1.32 (s, 6 H).

**EXAMPLE 12**

6-Difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-1,2,2,9-tetramethyl-8-pyridonof[5,6-g]quinoline (Compound 110, Structure 22 of Scheme III, where  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{difluoromethyl}$ ,  $R^4 = \text{F}$ )

- 5 This compound was prepared in a manner similar to that described for the preparation of Compound 109 (EXAMPLE 11) from Compound 108 (18.4 mg, 0.0590), paraformaldehyde (17.7 mg, 0.592 mmol, 10 equiv) and sodium cyanoborohydride (17.9 mg, 0.286 mmol, 4.8 equiv) in AcOH (3.0 mL) to afford 11 mg (57%) of Compound 110, a yellow solid, after purification by flash chromatography ( $\text{CH}_2\text{Cl}_2:\text{EtOAc}$ , 19:1). Data for
- 10 Compound 110:  $^1\text{H}$  NMR (400 MHz, acetone- $d_6$ ) 7.54 (s, 1 H), 7.36 (t,  $J = 7.36$  (t,  $J = 53.0$ , 1 H), 6.48 (s, 1 H), 3.71 (s, 3 H), 3.02 (s, 3 H), 2.75-2.85 (m, 2 H), 1.87 (t,  $J = 6.4$ , 2 H), 1.34 (s, 6 H).

**EXAMPLE 13**

- 15 7-Fluoro-1,2-dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridonof[5,6-g]quinoline (Compound 111, structure 27 of Scheme IV, where  $R^1 = \text{H}$ ,  $R^3 = \text{trifluoromethyl}$ ,  $R^4 = \text{F}$ ).

1-tert-Butyloxycarbamoyl-3-nitrobenzene (structure 24 of Scheme IV, where  $R^1 = \text{H}$ ,  $R^2 = t\text{-BuO}$ ).

- To a flame-dried 500 mL round-bottomed flask containing 3-nitroaniline (structure
- 20 23 of Scheme IV, where  $R^1 = \text{H}$ ) (20.0 g, 144.8 mmol) in 150 mL THF was added di-tert-butyl dicarbonate (31.60 g, 144.8 mmol, 1.00 equiv), and the mixture was cooled to 0 °C. 4-*N,N*-Dimethylaminopyridine (19.46 g, 159.3 mmol, 1.10 equiv) was added portionwise, and the mixture was allowed to warm to rt overnight. Ethyl acetate (400 mL) was added, and the mixture was washed with 1M  $\text{NaHSO}_4(\text{aq})$  (2 x 200 mL) and brine (200 mL), dried
- 25 ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 9:1) afforded 31.4 g (91%) of 1-tert-butyloxycarbamoyl-3-nitrobenzene as a white solid. Data for 1-tert-butyloxycarbamoyl-3-nitrobenzene:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 8.31 (dd, 1H,  $J = 2.2$ , 2.2, 2-H), 7.88 (dd, 1H,  $J = 7.9$ , 1.5, 4-H), 7.69 (br d, 1H,  $J \approx 7.8$ , 6-H), 7.44 (dd, 1H,  $J = 8.3$ , 8.1, 5-H), 6.74 (br s, 1H, NH), 1.54 [s, 9H,  $(\text{CH}_3)_3\text{CO}$ ].
- 30

3-*tert*-Butyloxycarbamoylaniline (structure 25 of Scheme IV, where  $R^1=H$ ,  $R^2=t$ -BuO).

To an oven-dried 1 L round-bottomed flask containing 1-*tert*-butyloxycarbamoyl-3-nitrobenzene (20.0 g, 83.9 mmol) in 500 mL 1:1 ethyl acetate/ethanol at rt was added 10% Pd on C (approx 1 mol%), and the mixture was stirred under an atmosphere of H<sub>2</sub> gas for 6 h. The reaction mixture was then filtered, and concentrated under diminished pressure to give 17.4 g (quantitative) of 3-*tert*-butyloxycarbamoylaniline as a white oily solid. Data for 3-*tert*-butyloxycarbamoylaniline: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.04 (dd, 1H,  $J = 8.0, 8.0$ , 5-H), 6.98 (br s, 1H, NH), 6.53 (dd, 1H,  $J = 7.9, 1.8$ , 4-H), 6.36 (m, 2H, 6,2-H), 3.66 (br s, 2H, NH<sub>2</sub>), 1.51 [s, 9H, (CH<sub>3</sub>)<sub>3</sub>CO].

7-*tert*-Butyloxycarbamoyl-1,2-dihydro-2,2,4-trimethylquinoline (structure 26 of Scheme IV, where  $R^1=H$ ,  $R^2=t$ -BuO).

To an oven-dried 1 L round-bottomed flask containing 3-*tert*-butyloxycarbamoylaniline (17.4 g, 83.5 mmol), MgSO<sub>4</sub> (50 g, 5 equiv), and 4-*tert*-butylcatechol (420 mg, 3 mol%) in 120 mL acetone (approx 0.75 M in the aniline) was added iodine (1.07 g, 5 mol%), and the mixture was heated to reflux for 8 h. The crude reaction mixture was then cooled to r.t., filtered through a bed of Celite™ on a fritted-glass funnel, rinsing with ethyl acetate, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, gradient elution) afforded 19.9 g (82%) of 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,4-trimethylquinoline as a white solid, which was further purified by recrystallization from acetonitrile to give white needles. Data for 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,4-trimethylquinoline: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 6.93 (d, 1H,  $J = 8.3$ , 5-H), 6.81 (br s, 1H, HNBoc), 6.34 (m, 2H, 6,8-H), 5.21 (d, 1H,  $J = 0.9$ , 3-H), 3.71 (br s, 1H, NH), 1.94 (d, 3H,  $J = 1.0$ , 4-CH<sub>3</sub>), 1.50 [s, 9H, (CH<sub>3</sub>)<sub>3</sub>CO], 1.24 [s, 6H, 2-(CH<sub>3</sub>)<sub>2</sub>].

7-Amino-1,2-dihydro-2,2,4-trimethylquinoline.

To an oven-dried 25 mL round-bottomed flask containing 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,4-trimethylquinoline (400 mg, 1.38 mmol) in 2 mL dichloromethane at 0 °C was added trifluoroacetic acid (1.06 mL, 10 equiv), and the mixture was allowed to warm to r.t.. After 3 h at r.t., the reaction mixture was diluted with 50 mL dichloromethane, transferring to a 125 mL erlynmeyer flask, and cooled to 0°C before neutralization to pH 8



with sat'd aqueous NaHCO<sub>3</sub>. The biphasic mixture was transferred to a separatory funnel, the layers were separated, and the organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure to afford a light reddish oil. The crude material thus obtained was of greater than 98% purity by <sup>1</sup>H NMR, and was carried on to the next step without further purification. While the 7-amino-quinoline obtained decomposed appreciably within a few hours upon standing at rt, ethanolic solutions could be stored at -20°C for 2-3 days without substantial adverse effect on the subsequent reaction outcome. Typically however, the material was stored in bulk as the crystalline Boc-protected amine, and portions were hydrolysed as needed. Data for 7-amino-1,2-dihydro-2,2,4-trimethylquinoline: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 6.86 (d, 1H, *J* = 8.2, 5-H), 5.99 (dd, 1H, *J* = 8.0, 2.3, 6-H), 5.79 (d, 1H, *J* = 2.0, 8-H), 5.12 (d, 1H, *J* = 1.4, 3-H), 3.53 (br s, 3H, NH<sub>2</sub>, NH), 1.93 (d, 3H, *J* = 1.2, 4-CH<sub>3</sub>), 1.24 [s, 6H, 2-(CH<sub>3</sub>)<sub>2</sub>].

7-Fluoro-1,2-dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline  
(Compound 111, structure 27 of Scheme IV, where R<sup>1</sup> = H, R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = F).

This compound was prepared in a manner similar to that described for Compound 102 (EXAMPLE 2) from 7-amino-1,2-dihydro-2,2,4-trimethylquinoline (174 mg, 0.924 mmol), ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate (205 mg, 1.02 mmol, 1.1 equiv), 4 angstrom molecular sieves (90 mgs, 52%) and ZnCl<sub>2</sub> (189 mg, 1.39 mmol, 1.5 equiv) in benzene (9.2 mL) followed by *p*-TsOH (44 mg, 0.23 mmol, 0.25 equiv) to afford 235 mg (76%) of Compound 111 after chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 23:2). Data for Compound 111: R<sub>f</sub> 0.30 (23:2 CH<sub>2</sub>Cl<sub>2</sub>:MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 12.58 (broad s, 1 H), 7.40 (broad s, 1 H), 6.42 (s, 1 H), 5.43 (s, 1 H), 4.41 (broad s, 1 H), 2.02 (d, *J* = 1.1, 3 H), 1.31 (s, 6 H).

#### EXAMPLE 14

7-Fluoro-1,2,3,4-tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline  
(Compound 112, Structure 30 of Scheme V, where R<sup>1</sup> = H, R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = F).

A solution of Compound 111 (4.0 mg, 0.012 mmol) in EtOAc (0.49 mL) and EtOH (0.49 mL) containing 10% Pd/C (1 mg, 25%) was stirred under an atmosphere of H<sub>2</sub> for 12 h. The reaction mixture was filtered through a pad of Celite and purified by silica gel

chromatography (CH<sub>2</sub>Cl<sub>2</sub>: EtOAc, 1:1) to afford 1.1 mg (28%) of Compound 112 as a yellow solid. Data for Compound 112: R<sub>f</sub> 0.44 (1:1 CH<sub>2</sub>Cl<sub>2</sub>: EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 11.94 (broad s, 1 H), 7.56 (s, 1 H), 6.38 (s, 1 H), 4.38 (broad s, 1 H), 2.90-3.00 (m, 1 H), 1.80 (dd, J = 12.6, 4.5, 1 H), 1.35-1.45 (m, 1 H), 1.39 (d, J = 6.7, 3 H), 1.28 (s, 3 H), 1.22 (s, 3 H).

### EXAMPLE 15

1,10-[1,3-dihydro-3-oxo-(2,1-isoxazoly)]-1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound 113, structure 31 of Scheme VI, where R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = H).

6-tert-Butyloxycarbamoyl-2-nitrotoluene (structure 24 of Scheme IV, where R<sup>1</sup> = Me, R<sup>2</sup> = *t*-BuO).

This compound was prepared from 2-methyl-3-nitroaniline (5.00 g, 32.8 mmol) in a manner similar to that described for 1-tert-butyloxycarbamoyl-3-nitrobenzene (EXAMPLE 13), affording 7.44 g (90%) of the desired carbamate as an off-white solid. Data for 6-tert-butyloxycarbamoyl-2-nitrotoluene: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.98 (br d, 1H, J Å 8.0 Hz, 5-H), 7.51 (br d, 1H, J Å 8.1 Hz, 3-H), 7.28 (dd, 1H, J = 7.6, 3.4 Hz, 4-H), 6.58 (br s, 1H, NH), 2.34 (s, 3H, 1-CH<sub>3</sub>), 1.53 [s, 9H, (CH<sub>3</sub>)<sub>3</sub>CO].

2-Amino-6-tert-butyloxycarbamoyltoluene (structure 25 of Scheme IV, where R<sup>1</sup> = Me, R<sup>2</sup> = *t*-BuO).

This compound was prepared from 6-tert-butyloxycarbamoyl-2-nitrotoluene (4.60 g, 18.2 mmol) in a manner similar to that described for 3-tert-butyloxycarbamoylaniline (EXAMPLE 13), affording 4.00 g (99%) of the desired aniline as a colorless oil. Data for 2-amino-6-tert-butyloxycarbamoyltoluene: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.04 and 6.81 (br δ of ABq, 2H, J<sub>AB</sub> = 8.0 Hz, J<sub>A</sub> = 0 Hz, J<sub>B</sub> = 7.9 Hz, 4,5-H), 6.49 (d, 1H, J = 8.3 Hz, 3-H), 6.26 (br s, 1H, NH), 3.61 (br s, 2H, NH<sub>2</sub>), 2.02 (s, 3H, 1-CH<sub>3</sub>), 1.51 [s, 9H, (CH<sub>3</sub>)<sub>3</sub>CO].

7-tert-Butyloxycarbamoyl-1,2-dihydro-2,2,4,8-tetramethylquinoline (structure 26 of Scheme IV, where R<sup>1</sup> = Me, R<sup>2</sup> = *t*-BuO).

This compound was prepared from 2-amino-6-tert-butyloxycarbamoyltoluene (4.00 g, 18.0 mmol) in a manner similar to that described for 7-tert-butyloxycarbamoyl-1,2-dihydro-2,2,4-trimethylquinoline (EXAMPLE 13), affording 4.56 g (84%) of the desired

dihydroquinoline as a white solid. Data for 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,4,8-tetramethylquinoline:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 6.94 and 6.88 (br ABq, 2H,  $J_{\text{AB}}$  Å 8.3 Hz, 6,5-H), 6.16 (br s, 1H,  $\text{HNBOc}$ ), 5.27 (s, 1H, 3-H), 3.61 [br s, 1H,  $(\text{CH}_3)_2\text{CNH}$ ], 2.04 (s, 3H, 8- $\text{CH}_3$ ), 1.97 (s, 3H, 4- $\text{CH}_3$ ), 1.50 [s, 9H,  $(\text{CH}_3)_3\text{CO}$ ], 1.28 [s, 6H, 2- $(\text{CH}_3)_2$ ].

5        7-Amino-1,2-dihydro-2,2,4,8-tetramethylquinoline.

Removal of the Boc protective group of 7-*tert*-butyloxycarbamoyl-1,2-dihydro-2,2,4,8-tetramethylquinoline (400 mg, 1.32 mmol) was effected in the manner similar to that described for 7-amino-1,2-dihydro-2,2,4-trimethylquinoline (EXAMPLE 13), affording 267 mg (quantitative) of the desired aniline as a light reddish oil. Data for 7-amino-1,2-dihydro-10 2,2,4,8-tetramethylquinoline:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 6.82 (d, 1H,  $J = 8.2$  Hz, 5-H), 6.08 (d, 1H,  $J = 8.1$  Hz, 6-H), 5.15 (d, 1H,  $J = 1.2$  Hz, 3-H), 3.56 (br s, 3H,  $\text{NH}_2$ ,  $\text{NH}$ ), 1.95 (d, 3H,  $J = 1.2$  Hz, 4- $\text{CH}_3$ ), 1.91 (s, 3H, 8- $\text{CH}_3$ ), 1.27 [s, 6H, 2- $(\text{CH}_3)_2$ ].

1,2-Dihydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*f*]quinoline (structure 27 of Scheme IV, where  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{trifluoromethyl}$ ,  $\text{R}^4 = \text{H}$ ).

15        This compound was prepared in a manner similar to that described for Compound 102 (EXAMPLE 2) with 7-amino-1,2-dihydro-2,2,4,8-tetramethylquinoline (100 mg, 0.49 mmol) and ethyl 4,4,4-trifluoroacetoacetate (107 mL, 0.73 mmol, 1.5 equiv), affording 75 mg (47%) of the desired 2-quinolone as a fluorescent-yellow solid. Data for 1,2-dihydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*f*]quinoline:  $^1\text{H}$  NMR (400 MHz, 20  $\text{CDCl}_3$ ) 9.23 (br s, 1H,  $\text{CONH}$ ), 7.37 (s, 1H, 5-H), 6.67 (s, 1H, 7-H), 5.45 (s, 1H, 3-H), 4.14 [br s, 1H,  $(\text{CH}_3)_2\text{CNH}$ ], 2.12 (s, 3H, 10- $\text{CH}_3$ ), 2.04 (d, 3H,  $J = 1.1$  Hz, 4- $\text{CH}_3$ ), 1.37 [s, 6H, 2- $(\text{CH}_3)_2$ ].

1,2,3,4-Tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (structure 30 of Scheme V, where  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{trifluoromethyl}$ ,  $\text{R}^4 = \text{H}$ ).

25        To a 50-mL round-bottomed flask containing 1,2-dihydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-*f*]quinoline (421 mg, 1.31 mmol) in 5 mL 1,2-dichloroethane was added triethylsilane (1.04 mL, 6.53 mmol, 5.0 equiv) and trifluoroacetic acid (0.50 mL, 6.53 mmol, 5.00 equiv), and the mixture was heated to reflux using an oil bath. After 12 h, the mixture was cooled to 0 °C and quenched by the addition of 25 mL 30 sat'd aqueous  $\text{NaHCO}_3$ . The resultant biphasic mixture was extracted with EtOAc (50 mL), and the organic solution was washed with 25 mL brine and dried over  $\text{Na}_2\text{SO}_4$ . The solvent

was removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 2:1) affording 398 mg (94%) of the desired 3,4-saturated analogue as a pale fluorescent-yellow solid. Data for 1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline: mp 239-40°C, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 9.70 (br s, 1H, CONH), 7.50 (s, 1H, 5-H), 6.68 (s, 1H, 7-H), 4.13 [br s, 1H, (CH<sub>3</sub>)<sub>2</sub>CNH], 3.00 (ddq, 1H, J = 12.9, 12.4, 6.3 Hz, 4-H), 2.15 (s, 3H, 10-CH<sub>3</sub>), 1.83 and 1.46 [dd of ABq, 2H, J<sub>AB</sub> = 13.0 Hz, J<sub>A</sub> = 5.3, 1.6 Hz (3-H<sub>eq</sub>), J<sub>B</sub> = 12.9, 0 Hz (3-H<sub>ax</sub>)], 1.40 (d, 3H, J = 6.6 Hz, 4-CH<sub>3</sub>), 1.36 and 1.25 [2s, 2 x 3H, 2-(CH<sub>3</sub>)<sub>2</sub>]. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 162.5, 144.9, 139.1, 137.1, 124.3, 122.7, 120.9, 113.8, 105.7, 101.6, 50.2, 43.5, 31.8, 28.9, 27.6, 20.1, 9.7. Anal. Calcd for C<sub>17</sub>H<sub>19</sub>F<sub>3</sub>N<sub>2</sub>O: C, 62.95; H, 5.90; N, 8.64. Found: C, 63.02; H, 6.01; N, 8.48.

1,10-[1,3-dihydro-3-oxo-(2,1-isoxazolyl)]-1,2,3,4-tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound 113).

To a 10-mL round-bottomed flask containing 1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (50.0 mg, 0.15 mmol) in 1.5 mL CH<sub>3</sub>CN at rt was added 0.8 mL 30% aqueous H<sub>2</sub>O<sub>2</sub> and 0.5 mL peracetic acid. The mixture was allowed to stir at rt 24 h, and was then transferred to a separatory funnel containing 40 mL CH<sub>2</sub>Cl<sub>2</sub>, 20 mL 10% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and 20 mL sat'd aqueous NaHCO<sub>3</sub>. The layers were separated, and the organic solution was washed with 20 mL brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (silica gel, 500 mm, hexanes/EtOAc, 1:1) to give 22.3 mg (41%) of the oxo-isoxazolyl-derivative as a bright purple solid. Data for Compound 113: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 9.70 (br s, 1H, CONH), 7.15 (s, 1H, 5-H), 6.58 (s, 1H, 7-H), 3.08 (m, 1H, 4-H), 2.13 and 2.07 [dd of ABq, 2H, J<sub>AB</sub> = 13.0 Hz, J<sub>A</sub> = 5.3, 1.6 Hz (3-H<sub>eq</sub>), J<sub>B</sub> = 12.9, 0 Hz (3-H<sub>ax</sub>)], 1.61 and 1.59 [2s, 2 x 3H, 2-(CH<sub>3</sub>)<sub>2</sub>], 1.46 (d, 3H, J = 6.6 Hz, 4-CH<sub>3</sub>).

**EXAMPLE 16**

7-Fluoro-1,2-dihydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound 114, structure 27 of Scheme IV, where R<sup>1</sup> = Me, R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = F).

This compound was prepared in manner similar to that described for Compound 102 (EXAMPLE 2) from 7-amino-1,2-dihydro-2,2,4,8-tetramethylquinoline (242 mg, 1.19

mmol) to afford Compound 114 (206 mg, 51%) as a yellow solid. Data for Compound 114: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 9.78 (br s, 1H, CONH), 7.40 (s, 1H, 5-H), 5.46 (s, 1H, 3-H), 4.10 [br s, 1H, (CH<sub>3</sub>)<sub>2</sub>CNH], 2.16 (s, 3H, 10-CH<sub>3</sub>), 2.04 (s, 3H, 4-CH<sub>3</sub>), 1.37 ppm [s, 6H, 2-(CH<sub>3</sub>)<sub>2</sub>].

5

### EXAMPLE 17

7-Fluoro-1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound 115, structure 30 of Scheme V, where R<sup>1</sup> = Me, R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = F).

10 This compound was prepared in a manner similar to that described for 1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (EXAMPLE 15) from Compound 114 (84 mg, 0.25 mmol), affording Compound 115 (57 mg, 68%) as a yellow solid. Data for Compound 115: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 10.21 (br s, 1H, CONH), 7.52 (s, 1H, 5-H), 4.06 [br s, 1H, (CH<sub>3</sub>)<sub>2</sub>CNH], 3.00 (ddq, 1H, J = 12.9, 12.4, 6.3  
15 Hz, 4-H), 2.19 (s, 3H, 10-CH<sub>3</sub>), 1.83 and 1.46 [dd of ABq, 2H, J<sub>AB</sub> = 13.0 Hz, J<sub>A</sub> = 5.3, 1.6 Hz (3-H<sub>eq</sub>), J<sub>B</sub> = 12.9, 0 Hz (3-H<sub>ax</sub>)], 1.39 (d, 3H, J = 6.6 Hz, 4-CH<sub>3</sub>), 1.36 and 1.24 [2s, 2 x 3H, 2-(CH<sub>3</sub>)<sub>2</sub>].

### EXAMPLE 18

20 7-Fluoro-1,2,3,4-tetrahydro-2,2,4,9,10-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound 116, structure 32 of Scheme VII, where R<sup>1</sup> = Me, R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = F).

This compound was prepared from 7-fluoro-1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline in the manner previously described for the  
25 methylation of the amide nitrogen (EXAMPLE 3) from Compound 115 (21 mg, 0.06 mmol), affording Compound 116 (18 mg, 85%) as a yellow solid. Data for Compound 116: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.67 (s, 1H, 5-H), 4.13 (s, 3H, 9-CH<sub>3</sub>), 3.98 [br s, 1H, (CH<sub>3</sub>)<sub>2</sub>CNH], 3.00 (ddq, 1H, J = 12.9, 12.4, 6.3 Hz, 4-H), 2.41 (s, 3H, 10-CH<sub>3</sub>), 1.83 and 1.54 [dd of ABq, 2H, J<sub>AB</sub> = 13.0 Hz, J<sub>A</sub> = 5.3, 1.6 Hz (3-H<sub>eq</sub>), J<sub>B</sub> = 12.9, 0 Hz (3-H<sub>ax</sub>)], 1.45  
30 (d, 3H, J = 6.6 Hz, 4-CH<sub>3</sub>), 1.36 and 1.25 [2s, 2 x 3H, 2-(CH<sub>3</sub>)<sub>2</sub>].

**EXAMPLE 19**

7-Fluoro-1,2,3,4-tetrahydro-1,2,2,4,10-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **117**, structure **33** of Scheme VII, where  $R^1 = \text{Me}$ ,  $R^3 =$   
5 trifluoromethyl,  $R^4 = \text{F}$ ).

This compound was prepared from 7-fluoro-1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (18 mg, 0.05 mmol) in the manner previously described for the methylation of the quinoline nitrogen (EXAMPLE 11), affording  
Compound **117** (17 mg, 91%) as a yellow solid. Data for Compound **117**:  $^1\text{H}$  NMR (400  
10 MHz,  $\text{CDCl}_3$ ) 10.34 (br s, 1H, CONH), 7.53 (s, 1H, 5-H), 3.62 (s, 3H, 1- $\text{CH}_3$ ), 3.00 (ddq, 1H,  $J = 12.9, 12.4, 6.3$  Hz, 4-H), 2.21 (s, 3H, 10- $\text{CH}_3$ ), 1.82 and 1.42 [dd of ABq, 2H,  $J_{\text{AB}} = 13.0$  Hz,  $J_{\text{A}} = 5.3, 1.6$  Hz (3- $\text{H}_{\text{eq}}$ ),  $J_{\text{B}} = 12.9, 0$  Hz (3- $\text{H}_{\text{ax}}$ )], 1.45 (d, 3H,  $J = 6.6$  Hz, 4- $\text{CH}_3$ ), 1.33 and 1.25 [2s, 2 x 3H, 2-( $\text{CH}_3$ )<sub>2</sub>].

15

**EXAMPLE 20**

1,2,3,4-Tetrahydro-1-hydroxy-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound **118**, structure **35** of Scheme VIII, where  $R^3 = \text{trifluoromethyl}$ ,  $F^4 = \text{H}$ ).

1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (structure **20** of Scheme III, where  $R^3 = \text{trifluoromethyl}$ ,  $F^4 = \text{H}$ ).

20 In a 50-mL r.b. flask, a solution of the 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline (EXAMPLE 7) (0.85 g) in EtOH (10 mL) was treated with ethyl 4,4,4-trifluoroacetoacetate (0.70 mL, 4.8 mmol) and  $\text{ZnCl}_2$  (0.96 g, 7.0 mmol, 1.5 equiv) and heated to reflux for 18 h. Two major products are observed by TLC (30:1  $\text{CH}_2\text{Cl}_2$ :MeOH,  $R_f$  0.85 and  $R_f$  0.35). The reaction mixture was allowed to cool to rt and the bulk of the  
25 solvent was removed in vacuo. The residue was dissolved in EtOAc (100 mL) and washed with  $\text{H}_2\text{O}$  (3 x 80 mL) and brine (1 x 100 mL). The aqueous layers were extracted with EtOAc (2 x 100 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ), filtered through a pad of Celite, and the pad was rinsed with EtOAc (200 mL). The filtrate was concentrated and purified by silica gel chromatography ( $\text{CH}_2\text{Cl}_2$ :MeOH, 60:1 to 15:1 gradient). The  
30 lower major band afforded 0.74 g (52%) of 1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline as a yellow powder. Data for 1,2,3,4-

tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline: <sup>1</sup>H NMR (400 MHz, DMSO *d*<sub>6</sub>) 11.70 (s, 1H), 7.18 (s, 1H), 6.85 (s, 1H), 6.35 (s, 1H), 2.65 (t, *J* = 6.6, 2H), 1.61 (t, *J* = 6.6, 2H), 1.17 (s, 6H).

5     1,2,3,4-Tetrahydro-1-hydroxy-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 118, structure 35 of Scheme VIII, where R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = trifluoromethyl, F<sup>4</sup> = H).

To a 10-mL round-bottomed flask containing 1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (40 mg, 0.13 mmol) in 1.0 mL CH<sub>3</sub>CN at rt was added 0.5 mL 30% aqueous H<sub>2</sub>O<sub>2</sub> and 0.3 mL peracetic acid. The mixture was allowed to stir at rt 24 h, and was then transferred to a separatory funnel containing 30 mL CH<sub>2</sub>Cl<sub>2</sub>, 15 mL 10% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and 15 mL sat'd aqueous NaHCO<sub>3</sub>. The layers were separated, and the organic solution was washed with 15 mL brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (silica gel, 500 mm, hexanes/EtOAc, 1:1) to give 27 mg (65%) of the N-hydroxy-derivative as a bright purple solid. Data for Compound 118: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 9.88 (br s, 1H, CONH), 7.26 (s, 1H, 5-H), 7.14 (s, 1H, 7-H), 6.50 (s, 1H, 10-H) 2.96 (dd, 2H, *J* = 7.0, 6.1, 4-H), 2.23 (dd, 2H, *J* = 6.8, 6.8, 3-H), 1.32 [s, 6H, 2-(CH<sub>3</sub>)<sub>2</sub>].

#### EXAMPLE 21

20     1,2,3,4-Tetrahydro-1-hydroxy-2,2,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (Compound 119, structure 36 of Scheme VIII, where R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = trifluoromethyl, F<sup>4</sup> = H).

This compound was prepared by the methylation of 1,2,3,4-tetrahydro-1-hydroxy-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-*g*]quinoline (16 mg, 0.05 mmol) as previously described (EXAMPLE 2), affording 12 mg (73%) of the methylated derivative as a bright purple solid. Data for Compound 119: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.26 (s, 1H, 5-H), 7.18 (s, 1H, 7-H), 6.44 (s, 1H, 10-H) 3.97 (s, 3H, 9-CH<sub>3</sub>), 2.90 (dd, 2H, *J* = 7.0, 6.1, 4-H), 2.21 (dd, 2H, *J* = 6.8, 6.8, 3-H), 1.58 [s, 6H, 2-(CH<sub>3</sub>)<sub>2</sub>].

**EXAMPLE 22**

2,2-Diethyl-7-fluoro-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyridono[5,6-g]quinoline  
(Compound 120, Structure 20 of Scheme III, where  $R^1 = R^2 = \text{Et}$ ,  $R^3 = \text{trifluoromethyl}$ ,  $R^4 = \text{F}$ ).

5     3-Ethylpent-1-yn-3-yl acetate (structure 14 of Scheme III, where  $R^1 = R^2 = \text{Et}$ ).

In a 250-mL r.b., a solution of 3-ethyl-1-pentyn-3-ol (11.5 g, 102 mmol) in pyridine (10.2 mL) was treated sequentially with  $\text{Et}_3\text{N}$  (15.0 mL, 0.107 mol, 1.4 equiv), acetic anhydride (13.5 mL, 143 mmol, 1.4 equiv), and DMAP (1.25 g, 10.2 mmol, 10.0 mol%).

The reaction mixture was stirred at rt for 5 d, then treated with MeOH (5 mL) and stirred for  
10     1 h. The mixture was partitioned between ether (100 mL) and water (100 mL), and the aqueous layer was extracted with ether (100 mL). The organic layers were washed sequentially with 2 N  $\text{NaHSO}_4$  and brine (50 mL), dried ( $\text{MgSO}_4$ ), filtered, and concentrated. Distillation under reduced pressure afforded 11.8 g (58.8%) 3-ethylpent-1-yn-3-yl acetate, a colorless oil, bp 38-39°C @ 15 mm Hg. Data for 3-ethylpent-1-yn-3-yl  
15     acetate:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 2.54 (s, 1 H), 2.03 (s, 3 H), 1.96-2.08 (m, 2 H), 1.84-1.95 (m, 2 H), 0.97 (t,  $J = 7.4$ , 6 H).

2-Ethyl-1-pentyn-3-yl(phenyl)amine (structure 16 of Scheme III, where  $R^1 = R^2 = \text{Et}$ ).

This compound was prepared in a manner similar to that described for Compound 4  
20     (Example 1) from aniline (4.10 g, 44.0 mmol, 1.1 equiv), CuCl (0.396 g, 4.00 mmol, 10 mol%), 3-ethylpent-1-yn-3-yl acetate (6.17 g, 40 mmol) and  $\text{Et}_3\text{N}$  (4.45 g, 44.0 mmol, 1.1 equiv) in THF (100 mL) to afford 5.11 g (68.2%) of 2-ethyl-1-pentyn-3-yl(phenyl)amine after flash chromatography (hexanes:EtOAc, 16:1). Data for 2-ethyl-1-pentyn-3-yl(phenyl)amine:  $R_f$  0.28 (16:1 hexanes:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.15-7.22  
25     (m, 2 H), 6.96 (dd,  $J = 8.5$ , 1.0, 2 H), 6.78 (t,  $J = 7.4$ , 1 H), 3.58 (broad s, 1 H), 2.44 (s, 1 H), 1.75-1.94 (m, 4 H), 1.02 (t,  $J = 7.5$ , 6 H).

2,2-Diethyl-1,2-dihydroquinoline (structure 17 of Scheme III, where  $R^1 = R^2 = \text{Et}$ ).

This compound was prepared in a manner similar to that described for 1,2-Dihydro-2,2-dimethylquinoline (structure 17 of Scheme III, where  $R^1 = R^2 = \text{Me}$ ) from 2-ethyl-1-pentyn-3-yl(phenyl)amine (3.00 g, 16.0 mmol) and CuCl (0.190 g, 1.92 mmol) in THF to  
30     afford 1.51 g (50%) of 2,2-diethyl-1,2-dihydroquinoline after flash chromatography



(hexanes:EtOAc, 16:1). Data for 2,2-diethyl-1,2-dihydroquinoline:  $R_f$  0.44 (16:1 hexanes:EtOAc;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 6.85-6.95 (m, 1 H), 6.81 (d,  $J = 7.3$ , 1 H), 6.48 (t,  $J = 7.3$ , 1 H), 6.36 (d,  $J = 9.9$ , 1 H), 5.21 (d,  $J = 9.9$ , 1 H), 3.39 (broad s, 1 H), 1.35-1.55 (m, 4 H), 0.93 (t,  $J = 7.5$ , 6 H).

5        2,2-Diethyl-1,2,3,4-tetrahydroquinoline (structure 18 of Scheme III, where  $R^1 = R^2 = \text{Et}$ ).

This compound was prepared in a manner similar to that described for 1,2,3,4-tetrahydro-2,2-dimethylquinoline (structure 18 of Scheme III, where  $R^1 = R^2 = \text{Me}$ ) from 2,2-diethyl-1,2-dihydroquinoline (1.46 g, 7.80 mmol) and 10% Pd/C (146 mg, 10% by weight) in EtOAc (18.7 mL) to afford 1.04 g (70%) 2,2-diethyl-1,2,3,4-tetrahydroquinoline after flash chromatography (hexanes:EtOAc, 97:3). Data for 2,2-diethyl-1,2,3,4-tetrahydroquinoline:  $R_f$  0.43 (24:1 hexanes:ethyl acetate);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 6.90-7.00 (m, 2 H), 6.57 (td,  $J = 7.3$ , 1.0, 1 H), 6.46 (dd,  $J = 8.4$ , 1.0, 1 H), 3.63 (broad s, 1 H), 2.72 (t,  $J = 6.7$ , 2 H), 1.69 (t,  $J = 6.7$ , 2 H), 1.38-1.53 (m, 4 H), 0.86 (t,  $J = 7.4$ , 6 H).

15        2,2-Diethyl-1,2,3,4-tetrahydro-7-nitroquinoline.

This compound was prepared in a manner similar to that described for 1,2,3,4-tetrahydro-2,2-dimethyl-7-nitroquinoline (Scheme III) from for 2,2-diethyl-1,2,3,4-tetrahydroquinoline (0.955 g, 5.04 mmol) and fuming  $\text{HNO}_3$  (0.32 g, 5.0 mmol) in concentrated sulfuric acid (10 mL) to afford 0.811 g (69%) of 2,2-diethyl-1,2,3,4-tetrahydro-7-nitroquinoline after chromatography (hexanes:EtOAc, 24:1). Data for 2,2-diethyl-1,2,3,4-tetrahydro-7-nitroquinoline:  $R_f$  0.43 (24:1 hexanes:ethyl acetate);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 7.38 (dd,  $J = 8.3$ , 2.3, 1 H), 7.29 (d,  $J = 2.3$ , 1 H), 7.04 (d,  $J = 8.3$ , 1 H), 4.00 (broad s, 1 H), 2.78 (t,  $J = 6.7$ , 2 H), 1.71 (t,  $J = 6.7$ , 2 H), 1.38-1.58 (m, 4 H), 0.88 (t,  $J = 7.4$ , 6 H).

25        7-Amino-2,2-diethyl-1,2,3,4-tetrahydroquinoline (structure 19 of Scheme III, where  $R^1 = R^2 = \text{Et}$ ).

This compound was prepared in a manner similar to that described for 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline (structure 19 of Scheme III, where  $R^1 = R^2 = \text{Me}$ ) from for 2,2-diethyl-1,2,3,4-tetrahydro-7-nitroquinoline (0.311 g, 1.33 mmol) and 10% Pd/C (31 mg, 10% by weight) in EtOAc (4.0 mL) and EtOH (4.0 mL) to afford 255 mg (94%) of 7-amino-2,2-diethyl-1,2,3,4-tetrahydroquinoline. Data for 7-amino-2,2-diethyl-1,2,3,4-tetrahydroquinoline:  $R_f$  0.26 (4:1 hexanes:ethyl acetate);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 6.77

(d,  $J = 7.9$  H, 1 H), 6.12 (dd,  $J = 7.9, 1.9$ , 1 H), 6.05 (d,  $J = 2.0$ , 1 H), 4.68 (broad s, 3 H), 2.62 (t,  $J = 6.7$ , 2 H), 1.67 (t,  $J = 6.7$ , 2 H), 1.38-1.55 (m, 4 H), 0.85 (t,  $J = 7.4$ , 6 H).

2,2-Diethyl-7-fluoro-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (Compound 120, Structure 20 of Scheme III, where  $R^1, R^2 = \text{Et}$ ,  $R^3 =$   
5 trifluoromethyl,  $R^4 = \text{F}$ ).

This compound was prepared in a manner similar to that described for Compound 102 (EXAMPLE 2) from 7-amino-2,2-diethyl-1,2,3,4-tetrahydroquinoline (0.100 g, 0.489 mmol), ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate (109 mg, 0.538 mmol, 1.1 equiv) and,  $\text{ZnCl}_2$  (100 mg, 0.734 mmol, 1.5 equiv) in benzene (4.9 mL) followed by  $p\text{-TsOH}$  (23.2  
10 mg, 0.122 mmol, 0.25 equiv) to afford 98 mg (58%) of Compound 120 after flash chromatography ( $\text{CH}_2\text{Cl}_2\text{:EtOAc}$ , 5:2). Data for Compound 120:  $R_f$  0.47 (5:2  $\text{CH}_2\text{Cl}_2\text{:EtOAc}$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 12.03 (broad s, 1 H), 7.40 (s, 1 H), 6.42 (s, 1 H), 4.40 (s, 1 H), 2.82 (t,  $J = 6.6$ , 2 H), 1.74 (t,  $J = 6.6$ , 2 H), 1.40-1.60 (m, 4 H), 0.93 (t,  $J =$   
15 7.4, 6 H).

### EXAMPLE 23

(*R/S*)-4-Ethyl-1-formyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline  
(Compound 121, structure 42 of Scheme IX, where  $R = \text{H}$ ).

#### 1,2,3,4-Tetrahydro-4-quinolinone.

20 In a 200 mL r.b. flask was introduced aniline (9.78 mL, 0.107 mol), acrylic acid (7.36 mL, 0.107 mol) and toluene (100 mL). The reaction mixture was stirred and heated at 100 °C for 16 h, cooled to rt and the solvent was removed *in vacuo* to give 10.34 g (60%) of the desired intermediate carboxylic acid that was used directly without further purification for the next step.

25 In a 500 mL r.b. flask was introduced the acid (10.34 g, 0.064 mol) and polyphosphoric acid (200 mL). The reaction mixture was stirred and heated at 100 °C for 16 h. The reaction mixture was cooled to rt, poured onto 700 mL of a 1:1 mixture of ice/water and neutralized slowly with NaOH. The aqueous phase was extracted with ethyl acetate (3 x 200 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed *in vacuo* to give a solid  
30 residue that was subjected to flash chromatography (silica gel, hexanes/ethyl acetate, 6:1) to afford 6.97 g (76%) of 1,2,3,4-tetrahydro-4-quinolinone. Data for 1,2,3,4-tetrahydro-4-

quinolinone:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84 (dd,  $J = 7.9$ , 1.1, 1H), 7.28 (ddd,  $J = 7.9$ , 7.9, 1.2, 1H), 6.72 (ddd,  $J = 8.1$ , 8.1, 0.8, 1H), 6.66 (d,  $J = 8.1$ , 1H), 4.49 (s, 1H), 3.56 (t,  $J = 6.9$ , 2H), 2.69 (t,  $J = 6.8$ , 2H).

1-tert-Butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone (structure 38 of Scheme

5 IX).

To a stirred solution of  $\text{Boc}_2\text{O}$  (10.05 g, 0.046 mol) and 1,2,3,4-tetrahydro-4-quinolinone (6.16 g, 0.042 mol) in THF (100 mL) at 0 °C was added slowly DMAP (5.11 g, 0.042 mol) in 100 mL of THF. The reaction mixture was stirred overnight, then water (75 mL) was added and the mixture was extracted with ethyl acetate (2 x 200 mL). The organic  
10 phase was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed *in vacuo* to give a solid residue that was subjected to flash chromatography (silica gel, hexanes/ethyl acetate, 8:2) which afforded 8.5 g (82%) of 1-tert-butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone. Data for 1-tert-butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (dd,  $J = 7.9$ , 1.7, 1H), 7.76 (d,  $J = 8.4$ , 1H), 7.49 (ddd,  $J = 7.5$ , 7.5, 1.7, 1H), 7.15  
15 (ddd,  $J = 8.0$ , 8.0, 0.9, 1H), 4.15 (t,  $J = 6.3$ , 2H), 2.76 (t,  $J = 6.6$ , 2H), 1.55 (s, 9H).

(R/S)-1-tert-Butyloxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline.

To a flame-dried 25-mL r.b. flask containing ethylmagnesium bromide (4.0 mL of a 3.0 M solution in  $\text{Et}_2\text{O}$ , 12.0 mmol, 3.0 equiv), at -10° C was added dropwise a solution of 1-tert-butyloxycarbonyl-1,2,3,4-tetrahydro-4-quinolinone (1.0 g, 4.0 mmol) in  $\text{Et}_2\text{O}$  (4 mL).  
20 The reaction mixture was stirred at -10° C for 15 min, then allowed to warm to rt over 10 min. A 1.0 M solution of  $\text{NaHSO}_4$  (10 mL) was then rapidly added. The resulting biphasic mixture was extracted with  $\text{EtOAc}$  (3 x 10 mL), and the combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes /  $\text{EtOAc}$ , 4:1), affording 800 mg (71%) of the desired  
25 product as a clear yellow oil ( $R_f$  0.14, hexanes /  $\text{EtOAc}$ , 4:1). Data for 1-tert-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (d, 1H,  $J = 8.4$ , 8-H), 7.47 (dd, 1H,  $J = 7.9$ , 1.7, 5-H), 7.21 (ddd, 1H,  $J = 7.4$ , 7.4, 1.6, 6-H), 7.09 (ddd, 1H,  $J = 7.8$ , 7.8, 1.1, 7-H), 4.03 (ddd, 1H,  $J = 12.9$ , 7.1, 4.7, 2-H), 3.47 (ddd, 1H,  $J = 13.1$ , 8.6, 4.3, 2-H), 2.11 (ddd, 1H,  $J = 13.5$ , 8.6, 4.8, 3-H), 1.86 (m, 3H,  
30 3-H,  $\text{CH}_2\text{CH}_3$ ), 1.52 [s, 9H,  $\text{C}(\text{CH}_3)_3$ ], 0.89 (t, 3H,  $J = 7.5$ ,  $\text{CH}_3$ ).

(R/S)-4-Ethyl-1,2,3,4-tetrahydroquinoline (structure 39 of Scheme IX).

To a flame-dried 100-mL rb flask containing 1-*tert*-butoxycarbonyl-4-ethyl-1,2,3,4-tetrahydro-4-hydroxyquinoline (800 mg, 2.88 mmol) in a 1:1 solution of EtOAc / EtOH (20 mL) at rt was added 10% Pd/C (approx. 1 mol %). After evacuation and flushing of the vessel three times with nitrogen, one drop of trifluoroacetic acid was added, the vessel evacuated once more, and the mixture stirred under an atmosphere of hydrogen for 16 h.

The reaction mixture was then filtered, and concentrated under reduced pressure. The residue was transferred to a 25-mL rb flask with CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and stirred at rt. TFA (1.2 mL) was added and the reaction was vented and stirred for 2 h at rt. A solution of sat'd.

NaHCO<sub>3</sub> (adjusted to pH 9 with 3.0 M NaOH) was added until the aqueous phase was approximately pH 9. The resulting aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), and the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure to yield 351 mg (71%) of a colorless oil, which turned blue on exposure to air (*R<sub>f</sub>* 0.40, hexanes / EtOAc, 2:1). Data for (R/S)-4-ethyl-1,2,3,4-tetrahydroquinoline: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.02 (d, 1H, *J* = 7.6, 8-H), 6.96 (ddd, 1H, *J* = 7.7, 7.7, 1.3, 7-H), 6.61 (ddd, 1H, *J* = 8.2, 8.2, 1.0, 6-H), 6.47 (d, 1H, *J* = 7.9, 5-H), 3.83 (br s, 1H, CH<sub>2</sub>NH), 3.31 (ddd, 1H, *J* = 11.3, 11.3, 3.6, 2-H), 3.25 (ddd, 1H, *J* = 9.7, 9.7, 4.8, 2-H), 2.65 (dddd, 1H, *J* = 10.1, 5.1, 5.1, 5.1, 4-H), 1.92 (dddd, 1H, *J* = 9.6, 4.7, 4.7, 4.7, 3-H), 1.82 (m, 1H, 3-H), 1.74 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 0.98 (t, 3H, *J* = 7.4, CH<sub>3</sub>).

(R/S)-7-Amino-4-ethyl-1,2,3,4-tetrahydroquinoline (structure 40 of Scheme IX).

A 25-mL rb flask containing (R/S)-4-ethyl-1,2,3,4-tetrahydroquinoline (340 mg, 2.1 mmol) was cooled to -10° C, and conc. H<sub>2</sub>SO<sub>4</sub> (5 mL) was added slowly. The resulting solution was warmed to rt to effect complete dissolution of the quinoline, then cooled again to -10° C and stirred vigorously. Fuming HNO<sub>3</sub> (85 µL) was added dropwise, slowly, and the reaction mixture turned dark red. After 10 min, the reaction mixture was poured onto cracked ice and diluted with water (5 mL). Sat'd NaHCO<sub>3</sub> (80 mL) was added, and the pH was adjusted to pH 9 with 3.0 M NaOH. This aqueous phase was extracted with EtOAc (3 x 75 mL), and the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure to yield a dark red oil. This crude material was placed into a 250-mL rb flask with 1:1 EtOAc / EtOH (40 mL) and 10% Pd on C (approx. 1 mol %). The vessel was evacuated

and flushed with nitrogen three times, then stirred under an atmosphere of hydrogen for 16 h, filtered, and concentrated under reduced pressure to yield a yellow oil, which was purified by flash chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub> / methanol, 9:1), affording 210 mg (57 %) of the desired product as a dark yellow oil (R<sub>f</sub> 0.50, CH<sub>2</sub>Cl<sub>2</sub> / MeOH, 9:1). Data for (*R/S*)-7-amino-4-ethyl-1,2,3,4-tetrahydroquinoline: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.81 (d, 1H, *J* = 8.1, 5-H), 6.02 (dd, 1H, *J* = 8.0, 2.2, 6-H), 5.84 (d, 1H, *J* = 2.3, 8-H), 3.48 (s, 2H, NH<sub>2</sub>), 3.27 (ddd, 1H, *J* = 11.1, 11.1, 3.5, 2-H), 3.20 (ddd, 1H, *J* = 9.8, 5.3, 4.5, 2-H), 2.55 (dddd, 1H, *J* = 10.2, 5.2, 5.2, 5.2, 4H), 1.90 (dddd, 1H, *J* = 9.6, 9.6, 9.6, 4.7, 3-H), 1.72 (m, 2H, 3-H, CH<sub>2</sub>CH<sub>3</sub>), 1.48 (m, 1H, CH<sub>2</sub>CH<sub>3</sub>), 0.96 (t, 3H, *J* = 7.4, CH<sub>3</sub>).

10        (*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (structure 41 of Scheme IX).

To a flame-dried 100-mL rb flask containing 7-amino-4-ethyl-1,2,3,4-tetrahydroquinoline (210 mg, 1.19 mmol), in ethanol (20 mL), at rt, was added ethyl-4,4,4-trifluoroacetoacetate (190 μL, 1.31 mmol, 1.1 equiv) followed by ZnCl<sub>2</sub> (244 mg, 1.79 mmol, 1.5 equiv). The reaction mixture was heated to reflux for 6 h, at which point all starting material had been consumed (by TLC analysis). The reaction mixture was cooled to rt, and the solvent removed under reduced pressure. Dichloromethane (20 mL) was added and the organic phase washed with sat'd NaHCO<sub>3</sub> (2 x 10 mL) and brine (1 x 10 mL), then dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. This crude product was purified by flash chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub> / MeOH, 15:1), affording 24.4 mg (7%) of the desired product as a yellow solid. Data for (*R/S*)-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline: R<sub>f</sub> 0.37, (CH<sub>2</sub>Cl<sub>2</sub> / MeOH, 9:1); <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.31 (s, 1H, 5-H), 6.47 (s, 1H, 7-H), 6.37 (s, 1H, 10-H), 3.34 (m, 2H, 2-H), 2.70 (m, 1H, 4-H), 1.88 (m, 2H, 3-H), 1.62 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.00 (t, 3H, *J* = 7.5, CH<sub>3</sub>).

25        (*R/S*)-4-Ethyl-1-formyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (Compound 121, structure 42, Scheme IX, where R = H).

In a 5 mL r.b. flask, a mixture of (*R/S*)-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (27 mg, 0.091 mmol) in formic acid (0.14 mL, 3.6 mmol, 40 equiv) was treated with acetic anhydride (30 μL, 0.32 mmol, 3.5 equiv), and

the reaction mixture was stirred at room temperature overnight. The mixture was quenched with saturated aqueous  $\text{NaHCO}_3$  (25 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated to 21 mg (70%) of Compound **121**, a white solid. Data for Compound **121**:  $R_f$  0.51 (11.5:1  $\text{CH}_2\text{Cl}_2$ : MeOH);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  12.40 (s, 1 H, C(O)NH), 8.98 (s, 1 H, C(O)H), 7.63 (s, 1 H, 5-H), 7.21 (s, 1 H, 10-H), 7.01 (s, 1 H, 7-H), 3.85-3.95 (m, 1 H, 2-H), 3.75-3.85 (m, 1 H, 2-H), 2.75-2.85 (m, 1 H, 4-H), 1.90-2.05 (m, 2 H, 2 x 3-H), 1.70-1.80 (m, 1 H,  $\text{CHCH}_3$ ), 1.55-1.65 (m, 1 H,  $\text{CHCH}_3$ ), 1.02 (t,  $J = 7.4$  Hz, 3 H,  $\text{CH}_3$ ).

10

**EXAMPLE 24**

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-1-(trifluoroacetyl)-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline (Compound **122**, structure **42**, Scheme IX, where  $R = \text{CF}_3$ ).

In a 5.0 mL r.b. flask, a mixture of (*R/S*)-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline (11.3 mg, 0.038 mmol), triethylamine (6.4  $\mu\text{L}$ , 0.046 mmol), and  $\text{CH}_2\text{Cl}_2$  (2.0 mL) was treated with trifluoroacetic anhydride (6.5  $\mu\text{L}$ , 0.046 mmol) and stirred for 24 h at rt. The mixture was then partitioned with  $\text{H}_2\text{O}$  (10 mL) and  $\text{CH}_2\text{Cl}_2$  (10 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 15 mL), and the combined organic layers were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) filtered, and concentrated to a yellow solid. Purification by flash chromatography (2 x 15 cm column, hexane:EtOAc, 1:1) afforded 7.6 mg (50%) of Compound **122**, a light yellow solid. Data for compound **122**:  $R_f$  0.48 (11.5:1  $\text{CH}_2\text{Cl}_2$ : MeOH);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.72 (broad s, 1 H, C(O)NH), 7.77 (broad s, 1 H, 10-H), 7.67 (s, 1 H, 5-H), 7.08 (s, 1 H, 7-H), 4.00-4.10 (m, 1 H, 2-H), 3.72-3.82 (m, 1 H, 2-H), 2.83-2.93 (m, 1 H, 4-H), 2.19-2.29 (m, 1 H, 3-H), 1.75-1.94 (m, 2 H, 3-H,  $\text{CHCH}_3$ ), 1.58-1.67 (m, 1 H,  $\text{CHCH}_3$ ), 1.00 (t,  $J = 7.4$  Hz, 3 H,  $\text{CH}_3$ ).

25

**EXAMPLE 25**

(*R/S*)-1-Acetyl-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline (Compound **123**, structure **42**, Scheme IX, where  $R = \text{Me}$ ).

In a 25 mL r.b. flask, a mixture of (*R/S*)-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline (116 mg, 0.39 mmol, 1.0 equiv) and triethylamine (0.218 mL, 1.56 mmol, 4.0 equiv) in dichloroethane (3.0 mL) was treated with

30

acetyl chloride (0.111 mL, 1.56 mmol, 4.0 equiv) dropwise, and stirred for 7 h. The mixture was partitioned with H<sub>2</sub>O (25 mL) and CH<sub>2</sub>Cl<sub>2</sub> (25 mL). The aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 25 mL), and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to a yellow solid. The <sup>1</sup>H NMR spectrum revealed that starting material remains. The crude material was treated with triethylamine (0.22 mL, 1.6 mmol, 4.0 equiv) and acetyl chloride (42 μL, 0.58 mmol, 1.5 equiv) in dichloroethane (7.0 mL). After 8 h, the mixture was partitioned with H<sub>2</sub>O (25 mL) and CH<sub>2</sub>Cl<sub>2</sub> (25 mL). The aqueous layers were extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 25 mL), and the combined extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to a yellow solid. The crude material (17.0 mg) was treated with K<sub>2</sub>CO<sub>3</sub> (6.9 mg, 0.050 mmol, 1.0 equiv) in MeOH for 15 minutes. The reaction mixture was partitioned with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and pH 7 phosphate buffer (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated to a yellow solid. Purification by semi-preparative HPLC (ODS reverse phase column, 3:1 MeOH:water) afforded 2.4 mg (14%) Compound 123, a white solid. Data for compound 123: R<sub>f</sub> 0.23 (1:1 hexane:EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.25 (broad s, 1 H, C(O)NH), 7.60 (broad s, 1 H, 10-H), 7.58 (s, 1 H, 5-H), 6.99 (s, 1 H, 7-H), 3.88-3.98 (m, 1 H, 2-H), 3.70-3.80 (m, 1 H, 2-H), 2.70-2.80 (m, 1 H, 4-H), 2.36 (s, 3 H, C(O)CH<sub>3</sub>), 2.05-2.12 (m, 1 H, 3-H), 1.80-1.90 (m, 1 H), 1.70-1.80 (m, 1 H), 1.60-1.66 (m, 1 H), 1.01 (t, J = 7.4 Hz, 3 H, CH<sub>3</sub>).

20

#### EXAMPLE 26

(R/S)-4-Ethyl-1,2,3,4-tetrahydro-10-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline (Compound 124, structure 44 of Scheme X, where R<sup>1</sup> = Et, R<sup>2</sup> = H.

In a 15-mL r.b. flask, a mixture of (R/S)-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline (64.7 mg, 0.22 mmol) in H<sub>2</sub>SO<sub>4</sub> (2.0 mL) was cooled to 0 °C. Fuming HNO<sub>3</sub> (20.0 μL, 0.44 mmol, 2 equiv) diluted in H<sub>2</sub>SO<sub>4</sub> (0.4 mL) was added over 1.2 min, and warmed to rt over a period of 10 min. The mixture was poured into a mixture of ice (25 g) and K<sub>2</sub>CO<sub>3</sub> (7.0 g). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 25 mL), and the combined organic layers were washed with pH 7 phosphate buffer, dried (MgSO<sub>4</sub>), filtered, and concentrated to a yellow solid. Purification by flash chromatography (2 x 15 cm column, CH<sub>2</sub>Cl<sub>2</sub>: EtOAc, 9:1) afforded 5.1 mg (6%) of Compound 124, an orange solid. Data for Compound 124: R<sub>f</sub> 0.29 (9:1 CH<sub>2</sub>Cl<sub>2</sub>:EtOAc);

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.38 (broad s, 1 H, C(O)NH), 9.82 (broad s, 1 H, NH), 7.48 (s, 1 H, 5-H), 6.84 (s, 1 H, 7-H), 3.62-3.70 (m, 2 H, 2 x 2-H), 2.75-2.84 (m, 1 H, 4-H), 1.92-2.02 (m, 2 H, 2 x 3-H), 1.59-1.67 (m, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 1.01 (t, J = 7.4 Hz, 3 H, CH<sub>3</sub>).

5

**EXAMPLE 27**

1,2,3,4-Tetrahydro-2,2-dimethyl-10-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline  
(Compound 125, structure 44 of Scheme X, where R<sup>1</sup> = H, R<sup>2</sup> = Me) and 1,2,3,4-Tetrahydro-2,2-dimethyl-7,10-dinitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline  
(Compound 126, structure 45 of Scheme X, where R<sup>1</sup> = H, R<sup>2</sup> = Me).

10

1,2,3,4-Tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline  
(structure 20 of Scheme III, where R<sup>1</sup>, R<sup>2</sup> = Me, R<sup>3</sup> = trifluoromethyl, R<sup>4</sup> = H).

This compound was prepared in a manner similar to that described for Compound 102 (EXAMPLE 2) from 7-amino-1,2,3,4-tetrahydro-2,2-dimethylquinoline (2.35 g, 12 mmol), ethyl 4,4,4-trifluoroacetoacetate (2.15 g, 13 mmol, 1.1 equiv) and, ZnCl<sub>2</sub> (2.74 g, 20 mmol, 1.7 equiv) to afford 1.91 g (48%) of 1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline. Data for 1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline: <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 11.70 (s, 1 H), 7.18 (s, 1 H), 6.85 (s, 1 H), 6.35 (s, 1 H), 2.65 (t, J = 6.6 Hz, 2 H), 1.61 (t, J = 6.6 Hz, 2 H), 1.17 (s, 6 H).

20

1,2,3,4-Tetrahydro-2,2-dimethyl-10-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline (Compound 125, structure 44 of Scheme X, where R<sup>1</sup> = H, R<sup>2</sup> = Me) and 1,2,3,4-Tetrahydro-2,2-dimethyl-7,10-dinitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline (Compound 126, structure 45 of Scheme X, where R<sup>1</sup> = H, R<sup>2</sup> = Me).

This compound was prepared in a manner similar to that described for Compound 124 (EXAMPLE 26) from 1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline (65 mg, 0.22 mmol) and fuming HNO<sub>3</sub> (26 mL, 0.66 mmol, 3.0 equiv) in conc. H<sub>2</sub>SO<sub>4</sub> (1.4 mL) to afford 18 mg (24%) of Compound 125, an orange solid, and 19 mg (22%) of Compound 126, an orange solid. Data for Compound 125: R<sub>f</sub> 0.38 (11.5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.38 (broad s, 1 H, C(O)NH), 9.67 (broad s, 1 H, NH), 7.51 (s, 1 H, 5-H), 6.83 (s, 1 H, 7-H), 2.93 (t, J = 6.6 Hz, 2 H, benzylic CH<sub>2</sub>), 1.84 (t, J = 6.6 Hz, 2 H, 2 x 3-H), 1.44 (s, 6 H, 2 x (CH<sub>3</sub>)<sub>2</sub>). Data for Compound

30



126:  $R_f$  0.24 (2:1 hexanes:EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  12.85 (broad s, 1 H, C(O)NH), 9.83 (broad s, 1 H, NH), 7.53 (s, 1 H, 5-H), 2.96 (t,  $J = 6.7$  Hz, 2 H, benzylic  $\text{CH}_2$ ), 1.88 (t,  $J = 6.7$  Hz, 2 H, 2 x 3-H), 1.47 (s, 6 H, 2 x  $(\text{CH}_3)_2$ ).

5

### EXAMPLE 28

(*R/S*)-4-Ethyl-1,2,3,4-tetrahydro-1-nitro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline quinoline (Compound 127, structure 46 of Scheme X, where  $R^1 = \text{Et}$ ,  $R^2 = \text{H}$ ).

In a 15-mL r.b. flask, a mixture of (*R/S*)-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-*g*]quinoline (50.0 mg, 0.17 mmol) and  $\text{H}_2\text{SO}_4$  (2.0 mL) was cooled to 2°C. Fuming  $\text{HNO}_3$  (15.0  $\mu\text{L}$ , 0.33 mmol, 2 equiv) diluted in  $\text{H}_2\text{SO}_4$  (0.5 mL) was added over a period of 2.0 min, and stirred at 4 °C for 45 min, then poured into a mixture of ice (25 g) and  $\text{K}_2\text{CO}_3$  (6.0 g). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 25 mL), and the combined organic layers were washed with pH 7 phosphate buffer, dried ( $\text{MgSO}_4$ ), filtered, and concentrated to a yellow solid. Purification by flash chromatography (2 x 15 cm column,  $\text{CH}_2\text{Cl}_2$ : EtOAc, 9:1) afforded 10.2 mg (18%) of Compound 127, an orange solid, and 8.1 mg (14%) of Compound 124, an orange solid, and. Data for Compound 127:  $R_f$  0.14 (9:1  $\text{CH}_2\text{Cl}_2$ :EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  12.32 (broad s, 1 H, C(O)NH), 8.17 (s, 1 H, 10-H), 7.66 (s, 1 H, 5-H), 7.06 (s, 1 H, 7-H), 4.09 (dt,  $J = 15.0, 4.9$  Hz, 1 H, 2-H), 3.71 (ddd,  $J = 15.5, 10.0, 6.1$  Hz, 1 H, 2-H), 2.85-2.92 (m, 1 H, 4-H), 2.00-2.10 (m, 2 H, 2 x 3-H), 1.63-1.72 (m, 1 H,  $\text{CHCH}_3$ ), 1.53-1.61 (m, 1 H,  $\text{CHCH}_3$ ), 1.02 (t,  $J = 7.4$  Hz, 3 H).

### Steroid Receptor Activity

Utilizing the "cis-trans" or "co-transfection" assay described by Evans et al., Science, 240:889-95 (May 13, 1988), the disclosure of which is herein incorporated by reference, the compounds of the present invention were tested and found to have strong, specific activity as both agonists, partial agonists and antagonists of AR. This assay is described in further detail in U.S. Patent Nos. 4,981,784 and 5,071,773, the disclosures of which are incorporated herein by reference.

The co-transfection assay provides a method for identifying functional agonists and partial agonists which mimic, or antagonists which inhibit, the effect of native hormones, and quantifying their activity for responsive IR proteins. In this regard, the co-transfection

assay mimics an *in vivo* system in the laboratory. Importantly, activity in the co-transfection assay correlates very well with known *in vivo* activity, such that the co-transfection assay functions as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology. See, e.g., T. Berger et al. 41 *J. Steroid Biochem. Molec. Biol.* 773 (1992),  
5 the disclosure of which is herein incorporated by reference.

In the co-transfection assay, a cloned cDNA for an IR (e.g., human PR, AR or GR) under the control of a constitutive promoter (e.g., the SV 40 promoter) is introduced by transfection (a procedure to induce cells to take up foreign genes) into a background cell substantially devoid of endogenous IRs. This introduced gene directs the recipient cells to  
10 make the IR protein of interest. A second gene is also introduced (co-transfected) into the same cells in conjunction with the IR gene. This second gene, comprising the cDNA for a reporter protein, such as firefly luciferase (LUC), controlled by an appropriate hormone responsive promoter containing a hormone response element (HRE). This reporter plasmid  
15 functions as a reporter for the transcription-modulating activity of the target IR. Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally expressed by a gene under control of the target receptor and its native hormone.

The co-transfection assay can detect small molecule agonists or antagonists of target IRs. Exposing the transfected cells to an agonist ligand compound increases reporter activity in the transfected cells. This activity can be conveniently measured, e.g., by  
20 increasing luciferase production, which reflects compound-dependent, IR-mediated increases in reporter transcription. To detect antagonists, the co-transfection assay is carried out in the presence of a constant concentration of an agonist to the target IR (e.g., progesterone for PR) known to induce a defined reporter signal. Increasing concentrations of a suspected antagonist will decrease the reporter signal (e.g., luciferase production). The  
25 co-transfection assay is therefore useful to detect both agonists and antagonists of specific IRs. Furthermore, it determines not only whether a compound interacts with a particular IR, but whether this interaction mimics (agonizes) or blocks (antagonizes) the effects of the native regulatory molecules on target gene expression, as well as the specificity and strength of this interaction.

30 The activity of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the co-transfection assay, and in standard IR binding assays, according to the following illustrative Examples.

**EXAMPLE 29****Co-transfection assay**

CV-1 cells (African green monkey kidney fibroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum then transferred to 96-well microtiter plates one day prior to transfection.

To determine AR agonist and antagonist activity of the compounds of the present invention, the CV-1 cells were transiently transfected by calcium phosphate coprecipitation according to the procedure of Berger et al., 41 *J. Steroid Biochem. Mol. Biol.*, 733 (1992) with the following plasmids: pShAR (5 ng/well), MTV-LUC reporter (100 ng/well), pRS- $\beta$ -Gal (50 ng/well) and filler DNA (pGEM; 45 ng/well). The receptor plasmid, pRShAR, contains the human AR under constitutive control of the SV-40 promoter, as more fully described in J.A. Simental et al., "Transcriptional activation and nuclear targeting signals of the human androgen receptor", 266 *J. Biol. Chem.*, 510 (1991).

The reporter plasmid, MTV-LUC, contains the cDNA for firefly luciferase (LUC) under control of the mouse mammary tumor virus (MTV) long terminal repeat, a conditional promoter containing an androgen response element. See e.g., Berger et al. *supra*. In addition, pRS- $\beta$ -Gal, coding for constitutive expression of *E. coli*  $\beta$ -galactosidase ( $\beta$ -Gal), was included as an internal control for evaluation of transfection efficiency and compound toxicity.

Six hours after transfection, media was removed and the cells were washed with phosphate-buffered saline (PBS). Media containing reference compounds (i.e. progesterone as a PR agonist, mifepristone ((11 $\beta$ ,17 $\beta$ )-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one: RU486; Roussel Uclaf) as a PR antagonist; dihydrotestosterone (DHT; Sigma Chemical) as an AR agonist and 2-OH-flutamide (the active metabolite of 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]pronanamide; Schering-Plough) as an AR antagonist; estradiol (Sigma) as an ER agonist and ICI 164,384 (N-butyl-3,17-dihydroxy-N-methyl-(7- $\alpha$ ,17- $\beta$ )-estra-1,3,5(10)-triene-7-undecanamide; ICI Americas) as an ER antagonist; dexamethasone (Sigma) as a GR agonist and RU486 as a GR antagonist; and aldosterone (Sigma) as a MR agonist and spironolactone ((7- $\alpha$ -[acetylthio]-17- $\alpha$ -hydroxy-3-oxopregn-4-ene-21-carboxylic acid gamma-lactone;

Sigma) as an MR antagonist) and/or the modulator compounds of the present invention in concentrations ranging from  $10^{-12}$  to  $10^{-5}$  M were added to the cells. Three to four replicates were used for each sample. Transfections and subsequent procedures were performed on a Biomek 1000 automated laboratory work station.

5 After 40 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC and  $\beta$ -Gal activities using a luminometer or spectrophotometer, respectively. For each replicate, the normalized response (NR) was calculated as:

---

$$\text{LUC response}/\beta\text{-Gal rate}$$

10 where  $\beta\text{-Gal rate} = \beta\text{-Gal} \cdot 1 \times 10^{-5} / \beta\text{-Gal incubation time}$ .

The mean and standard error of the mean (SEM) of the NR were calculated. Data was plotted as the response of the compound compared to the reference compounds over the  
15 range of the dose-response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response ( $EC_{50}$ ) was quantified. Agonist efficacy was a function (%) of LUC expression relative to the maximum LUC production by the reference agonist for PR, AR, ER, GR or MR. Antagonist activity was determined by testing the amount of LUC expression in the presence of a fixed amount of DHT as an AR agonist and  
20 progesterone as a PR agonist at the  $EC_{50}$  concentration. The concentration of test compound that inhibited 50% of LUC expression induced by the reference agonist was quantified ( $IC_{50}$ ). In addition, the efficacy of antagonists was determined as a function (%) of maximal inhibition.

#### 25 IR Binding assay

AR Binding: For the whole cell binding assay, COS-1 cells in 96-well microtiter plates containing DMEM-10% FBS were transfected as described above with the following plasmid DNA: pRShAR (2 ng/well), pRS- $\beta$ -Gal (50 ng/well) and pGEM (48 ng/well). Six hours after transfection, media was removed, the cells were washed with PBS and fresh  
30 media was added. The next day, the media was changed to DMEM-serum free to remove any endogenous ligand that might be complexed with the receptor in the cells.

After 24 hours in serum-free media, either a saturation analysis to determine the  $K_d$  for tritiated dihydrotestosterone ( $^3\text{H}$ -DHT) on human AR or a competitive binding assay to evaluate the ability of test compounds to compete with  $^3\text{H}$ -DHT for AR was performed. For the saturation analysis, media (DMEM-0.2% CA-FBS) containing  $^3\text{H}$ -DHT (in concentrations ranging from 12 nM to 0.24 nM) in the absence (total binding) or presence (non-specific binding) of a 100-fold molar excess of unlabeled DHT were added to the cells. For the competitive binding assay, media containing 1 nM  $^3\text{H}$ -DHT and test compounds in concentrations ranging from  $10^{-10}$  to  $10^{-6}$  M were added to the cells. Three replicates were used for each sample. After three hours at  $37^\circ\text{C}$ , an aliquot of the total binding media at each concentration of  $^3\text{H}$ -DHT was removed to estimate the amount of free  $^3\text{H}$ -DHT. The remaining media was removed, the cells were washed three times with PBS to remove unbound ligand, and cells were lysed with a Triton X-100-based buffer. The lysates were assayed for amount of bound  $^3\text{H}$ -DHT and  $\beta$ -Gal activity using a scintillation counter or spectrophotometer, respectively.

For the saturation analyses, the difference between the total binding and the nonspecific binding, normalized by the  $\beta$ -Gal rate, was defined as specific binding. The specific binding was evaluated by Scatchard analysis to determine the  $K_d$  for  $^3\text{H}$ -DHT. See e.g., D. Rodbard, "Mathematics and statistics of ligand assays: an illustrated guide" In: J. Langon and J.J. Clapp, eds., *Ligand Assay*, Masson Publishing U.S.A., Inc., New York, pp. 45-99, (1981), the disclosure of which is herein incorporated by reference. For the competition studies, the data was plotted as the amount of  $^3\text{H}$ -DHT (% of control in the absence of test compound) remaining over the range of the dose-response curve for a given compound. The concentration of test compound that inhibited 50% of the amount of  $^3\text{H}$ -DHT bound in the absence of competing ligand was quantified ( $\text{IC}_{50}$ ) after log-logit transformation. The  $K_i$  values were determined by application of the Cheng-Prusoff equation to the  $\text{IC}_{50}$  values, where:

$$K_i = \frac{\text{IC}_{50}}{(1 + [^3\text{H}\text{-DHT}]/K_d \text{ for } ^3\text{H}\text{-DHT})}$$

After correcting for non-specific binding, IC<sub>50</sub> values were determined. The IC<sub>50</sub> value is defined as the concentration of competing ligand needed to reduce specific binding by 50%. The IC<sub>50</sub> value was determined graphically from a log-logit plot of the data. The K<sub>i</sub> values were determined by application of the Cheng-Prusoff equivuation to the IC<sub>50</sub> values, the labeled ligand concentration and the K<sub>d</sub> of the labeled ligand.

The agonist, antagonist and binding activity assay results of selected androgen receptor modulator compounds of present invention and the standard reference compounds on AR, as well as the cross-reactivity of selected compounds on the PR, ER, MR and GR receptors, are shown in Tables 1-2 below. Efficacy is reported as the percent maximal response observed for each compound relative to the reference agonist and antagonist compounds indicated above. Also reported in Tables 1-2 for each compound is its antagonist potency or IC<sub>50</sub> (which is the concentration (nM), required to reduce the maximal response by 50%), its agonist potency or EC<sub>50</sub> (nM).

Table 1: Agonist, partial agonist, antagonist and binding activity of androgen receptor modulator compounds of present invention and the reference agonist compound, dihydrotestosterone (DHT), and reference antagonists compound, 2-hydroxyflutamide (Flut) and Casodex (Cas), on AR.

5

Cmpd No.	AR Agonist CV-1 Cells		AR Antagonist CV-1 Cells		AR Binding
	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)	K <sub>i</sub> (nM)
101	na	na	80	362	169
102	na	na	86	29	78
103	na	na	85	209	11
104	na	na	86	40	159
105	48	1560	31	4316	26
106	na	na	83	60	nt
107	na	na	79	47	110
109	na	na	86	12	nt
111	20	3452	50	49	804
112	nt	nt	49	20	nt
113	26	5122	48	1251	17
114	na	na	90	203	na
115	na	na	88	101	107
116	na	na	20	1460	na
117	na	na	81	394	na
118	na	na	70	482	89
119	na	na	35	3689	62
120	nt	nt	61	25	nt
121	84	196	na	na	na
122	93	3	38	6500	23
123	103	33	na	na	6600
124	58	220	24	5000	na
125	na	na	73	1300	na
126	na	na	44	5200	na
127	64	110	33	6	300
Flut	na	na	83	25	58
Cas	na	na	81	201	96
DHT	100	6	na	na	5

na = not active (i.e. efficacy of <20 and potency of >10,000)

nt = not tested

Table 2: Overall agonist and antagonist potency of selected androgen receptor modulator compounds of present invention and the reference agonist and antagonist compounds shown in Table 1 on PR, AR, ER, GR and MR.

Cmpd	PR Potency		AR Potency		ER Potency		GR Potency	MR Potency
No.	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Antag (nM)	Antag (nM)
101	na	na	na	362	na	na	na	na
102	na	398	na	29	na	na	na	na
103	na	5938	na	209	na	na	na	1586
104	na	800	na	40	nt	nt	nt	nt
105	na	160	1560	4316	na	34	na	2256
Prog	4	na	1300	na	na	na	na	nt
RU486	na	0.1	na	12	na	1500	0.7	1100
DHT	na	1800	6	na	1700	na	na	nt
Flut	na	1900	na	26	na	na	na	na
Estr	nt	nt	na	na	7	na	na	nt
ICI 164	na	na	na	na	na	160	na	na
Spir	nt	268	nt	nt	na	na	2000	25

na=not active (i.e., efficacy of >20 and potency of >10,000); nt=not tested

As can be seen in the Tables, Compounds 109 and 112 are highly selective AR antagonists, while Compounds 105, 111 and 113 are mixed AR agonists/antagonists.

- 10 Importantly, these AR Compounds show very little or no cross reactivity on other sex steroid receptors. In contrast, the known PR antagonist, RU486, shows strong cross reactivity on both GR and AR, showing essentially equivaal potency as both a PR and GR antagonist, and strong activity as an AR antagonist.

15

### EXAMPLE 30

Mouse Renal Ornithine Decarboxylase (ODC) Activity as an *in vivo* assay for determining the activity of AR Modulators

20

Ornithine Decarboxylase (ODC) is the first rate-limiting enzyme for polyamine synthesis and catalyzes conversion of L-ornithine to putrescine, releasing CO<sub>2</sub>. It is a constitutive enzyme present in all cells and tissues. ODC concentration is very low in quiescent cells; but, as part of a growth response, it increases many-fold within hours of exposure to trophic stimuli, such as hormones, drugs, and growth factors. See G.



Scalabrino, et al. "Polyamines and Mammalian Hormones", *Mol. Cell. Endocrinol.* 77:1-35, 1991.

This enzyme in the mouse kidney is specifically stimulated by androgens, but not by estrogen, progesterone or glucocorticoids. See O. A. Janne, et al. "Ornithine

- 5 Decarboxylase mRNA in Mouse Kidney: A Low Abundance Gene Product Regulated by Androgens with Rapid Kinetics", *Ann New York Academy of Sciences* 438:72-84, 1984 and J. F. Catterall, et al. "Regulation of Gene Expression by Androgens in Murine Kidney", *Rec. Prog. Hor. Res.* 42:71-109, 1986. Androgen induction of ODC activity and gene expression occurs rapidly, becoming maximally stimulated within 24 hr of a single dose of testosterone. Therefore, it is was used as an acute assay to determine the androgen specific response of compounds, including compounds of the present invention, *in vivo*.
- 10

In this assay, castrated male ICR mice (~ 30 g, 5 - 6 week-old) were grouped in fours and treated for 1 or 3 days as follows:

- 1) Control vehicle
- 15 2) Testosterone propionate (TP) (0.01-1.0 mg/mouse or 0.3-30 mg/kg, s.c.)
- 3) TP (3 mg/kg, s.c.) plus a reference compound or a compound of the present invention (30-90 mg/kg, orally/s.c.) to demonstrate antagonist activity, or
- 4) A compound of the present invention alone (30-90 mg/kg, orally/s.c.) to demonstrate AR agonist activity

- 20 The animals are sacrificed 24 hr after last dosing, and the pair of kidneys were collected and homogenized. The homogenates were centrifuged to get supernatant (cytosol), which was incubated with [<sup>3</sup>H]ornithine for 1 hour. The activity of this enzyme was measured by a titrimetric analysis of the rate of [<sup>3</sup>H]putrescine production. Results were expressed as femtomoles of [<sup>3</sup>H]putrescine formed per mg of protein per hour. R.
- 25 Djurhuus "Ornithine Decarboxylase (EC4.1.1.17) Assay Based Upon the Retention of Putrescine by a Strong Cation-Exchange Paper", *Anal. Biochem.* 113:352-355, 1981.

#### AR agonist mode:

- 30 Testosterone propionate (TP) induced the ODC activity in a dose-dependent manner within the doses of 0.01 to 1.0 mg/mouse. Even at the highest dose used (1 mg/mouse), the induced ODC activity was not saturated, which was a 700-fold increase compared to

castrated controls. Testosterone also showed similar stimulatory effects on ODC activities with less potency compared to TP (See Table 3). However, estradiol (0.02 mg/mouse) or progesterone (1 mg/mouse) did not show any stimulatory activity on this enzyme. The increase in ODC activity was accompanied by parallel, but lesser, changes in seminal vesicle weights. For example, TP (1.0 mg/mouse/day) resulted in a 700-fold increase in ODC activity, whereas increases in seminal vesicle weights were 4- to 5-fold.

Table 3. Androgenic Effects of Known Steroid compounds on Mouse Renal ODC activity (fold increase compared to castrated control).

10

known compound	Doses (mg/mouse)				
	0.01	0.03	0.1	0.3	1.0
Testosterone Propionate					
s.c. for 1 day			9.7	21.9	26.4
s.c. for 3 days	1	10	173	414	707
Testosterone					
s.c. for 3 days		1.5	2.3	17	135
Estradiol					
s.c. for 1 day		1.1			
Progesterone					
s.c. for 1 day					1.1

#### AR antagonist mode:

15

When testosterone propionate (0.1 mg/mouse) was used to induce the enzyme activity, the reference AR antagonists, flutamide, casodex and cyproterone acetate, inhibited this induction. Compounds of the present invention demonstrated AR antagonist activity in this assay model as shown in Table 4.

Table 4. Anti-Androgenic Effects on Mouse Renal ODC Activity

Compound	Dose <sup>a</sup> (mg/mouse)	% Inhibition of ODC Activity <sup>b</sup>		
		1 day s.c.	1 day p.o.	3 days p.o.
Flutamide	1	88.3	37.7	60.7
	3	98.1		92.0
Casodex	1	nt	97.0	98.9
Cyproterone acetate	1	nt	91.1	81.7
101	1	nt	31.7	26.2
102	1	25.4	- 5.2	nt
107	1	72	42	nt
120	1	52	46	nt

- a: The administration of all the compounds to castrated mice was combined with TP injection (0.1 mg/mouse/day, s.c.) for testing AR antagonists .
- b: % inhibition of ODC activity induced by testosterone propionate (TP). Here, TP group is full induction and 0% inhibition; while, castrated group served as basal line, indicating 100% inhibition. Negative number indicates that the presented compound had no AR antagonist effects, while the ODC activity was certain percentage higher than TP-treated group .

### Pharmacological and Other Applications

As will be discernible to those skilled in the art, the androgen receptor modulator compounds of the present invention can be readily utilized in pharmacological applications where AR antagonist or agonist activity is desired, and where it is desired to minimize cross reactivities with other steroid receptor related IRs. *In vivo* applications of the invention include administration of the disclosed compounds to mammalian subjects, and in particular to humans.

The following Example provides illustrative pharmaceutical composition formulations:

#### EXAMPLE 31

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
COMPOUND 101	140
Starch, dried	100
Magnesium stearate	<u>10</u>
Total	250 mg

The above ingredients are mixed and filled into hard gelatin capsules in 250 mg quantities.

A tablet is prepared using the ingredients below:

		Quantity (mg/tablet)
5	COMPOUND 101	140
	Cellulose, microcrystalline	200
	Silicon dioxide, fumed	10
10	Stearic acid	<u>10</u>
	Total	360 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Tablets, each containing 60 mg of active ingredient, are made as follows:

		Quantity (mg/tablet)
15	COMPOUND 101	60
	Starch	45
	Cellulose, microcrystalline	35
20	Polyvinylpyrrolidone (PVP) (as 10% solution in water)	4
	Sodium carboxymethyl starch (SCMS)	4.5
	Magnesium stearate	0.5
	Talc	<u>1.0</u>
25	Total	150 mg

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of PVP is mixed with the resultant powders, which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° C and passed through a No. 18 mesh U.S. sieve. The SCMS, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, and then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Suppositories, each containing 225 mg of active ingredient, may be made as follows:

35	COMPOUND 101	225 mg
	Saturated fatty acid glycerides	<u>2,000 mg</u>
	Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of normal 2g capacity and allowed to cool.

- 5        An intravenous formulation may be prepared as follows:

COMPOUND 101	100 mg
Isotonic saline	1,000 mL
Glycerol	100 mL

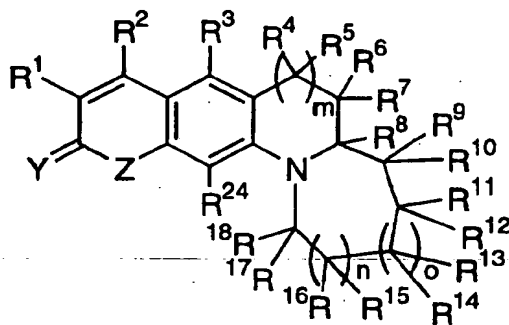
- 10       The compound is dissolved in the glycerol and then the solution is slowly diluted with isotonic saline. The solution of the above ingredients is then administered intravenously at a rate of 1 mL per minute to a patient.

- 15       While in accordance with the patent statutes, description of the preferred embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Various modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

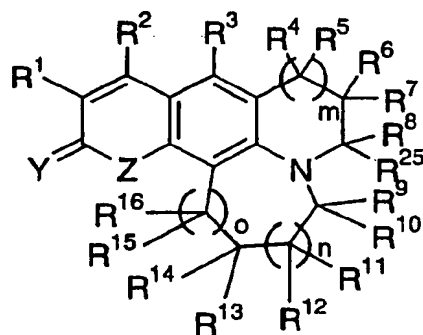
Consequently, for an understanding of the scope of the present invention, reference is made to the following claims.

What is claimed is:

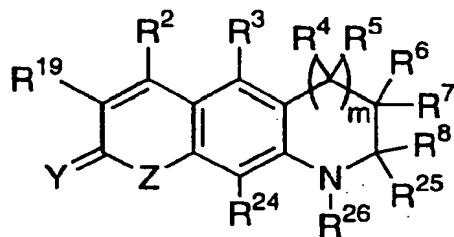
1. A compound having the formula:



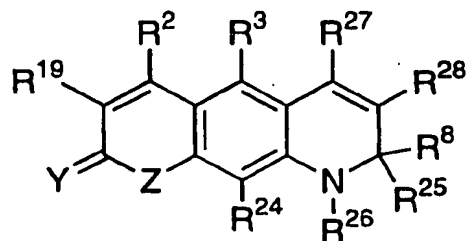
OR



OR

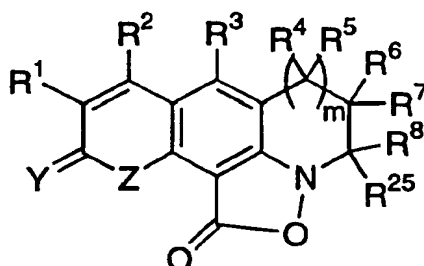


OR



(IV)

OR



(V)

5

wherein:

- $R^1$  is hydrogen, F, Cl, Br, I,  $\text{NO}_2$ ,  $\text{OR}^{20}$ ,  $\text{NR}^{21}\text{R}^{22}$ ,  $\text{SR}^{20}$ , a  $\text{C}_1$  -  $\text{C}_4$  alkyl or perhaloalkyl, or is an optionally substituted allyl, arylmethyl, alkynyl, alkenyl, aryl or heteroaryl, where  $R^{21}$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_6$  alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl,  $\text{SO}_2\text{R}^{23}$  or  $\text{S}(\text{O})\text{R}^{23}$ , where  $R^{23}$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_6$  alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl,  $R^{20}$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_6$  alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl, and  $R^{22}$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_4$  alkyl or perfluoroalkyl, aryl, heteroaryl, optionally substituted allyl or arylmethyl,  $\text{OR}^{20}$  or  $\text{NHR}^{21}$ ;
- $R^2$  is hydrogen, F, Br, Cl, a  $\text{C}_1$  -  $\text{C}_4$  alkyl or perhaloalkyl, aryl, heteroaryl,  $\text{CF}_3$ ,  $\text{CF}_2\text{H}$ ,  $\text{CFH}_2$ ,  $\text{CF}_2\text{OR}^{20}$ ,  $\text{CH}_2\text{OR}^{20}$ , or  $\text{OR}^{20}$ , where  $R^{20}$  has the same definition given above;
- $R^3$  is hydrogen, a  $\text{C}_1$  -  $\text{C}_4$  alkyl, F, Cl, Br, I,  $\text{OR}^{20}$ ,  $\text{NR}^{21}\text{R}^{22}$  or  $\text{SR}^{20}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;
- $R^4$  and  $R^5$  each independently are hydrogen, a  $\text{C}_1$  -  $\text{C}_4$  alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br,  $\text{OR}^{20}$  or  $\text{NR}^{21}\text{R}^{22}$ , or  $R^4$  and  $R^5$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $\text{OR}^{20}$  or  $\text{NR}^{21}\text{R}^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^6$  and  $R^7$  each independently are hydrogen, a  $C_1 - C_4$  alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , or  $R^6$  and  $R^7$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^8$  is hydrogen, a  $C_1 - C_{12}$  alkyl or perfluoroalkyl, hydroxymethyl, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl;

$R^9$  through  $R^{18}$  each independently are hydrogen, a  $C_1 - C_4$  alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , or any two of  $R^9$  through  $R^{18}$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^{19}$  is F,  $NO_2$  or  $SR^{20}$ , where  $R^{20}$  has the definition given above;

$R^{24}$  is hydrogen, a  $C_1 - C_4$  alkyl, F, Cl, Br, I,  $NO_2$ ,  $OR^{20}$ ,  $NR^{21}R^{22}$  or  $SR^{20}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^{25}$  is hydrogen, a  $C_1 - C_{12}$  alkyl, or perfluoroalkyl, hydroxymethyl, aryl, heteroaryl or optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or  $R^{25}$  and  $R^8$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^{26}$  is hydrogen, a  $C_1 - C_6$  alkyl or perfluoroalkyl,  $NO_2$ ,  $OR^{20}$ ,  $C(O)R^{20}$ ,  $C(O)OR^{20}$ ,  $C(O)NR^{21}R^{22}$ , or an optionally substituted aryl, heteroaryl, allyl or arylmethyl, where  $R^{20}$  through  $R^{22}$  have the definitions given above;

$R^{27}$  and  $R^{28}$  each independently are hydrogen, F, Cl, Br, I,  $OR^{20}$ ,  $NR^{21}R^{22}$ , a  $C_1 - C_4$  alkyl or perfluoroalkyl, heteroaryl, optionally substituted allyl, arylmethyl, alkynyl or alkenyl, or an aryl optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , or



$R^{27}$  and  $R^{28}$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above;

m is 0 or 1;

5 n is 0 or 1; and

o is 0 or 1;

Y is O or S;

Z is O, S, NH,  $NR^{22}$  or  $NCOR^{22}$ , where  $R^{22}$  has the same definition given above;

and

10 any two of  $R^4$  through  $R^8$ ,  $R^{25}$  and  $R^{28}$  taken together can form a three- to seven-membered ring optionally substituted with hydrogen, F, Cl, Br,  $OR^{20}$  or  $NR^{21}R^{22}$ , where  $R^{20}$  through  $R^{22}$  have the definitions given above.

2. A compound according to claim 1, wherein the compounds are androgen  
15 receptor modulators.

3. A compound according to claim 2, wherein the compounds are androgen  
receptor antagonists.

20 4. A compound according to claim 2, wherein the compounds are androgen  
receptor agonists.

5. A compound according to claim 2, wherein the compounds are androgen  
receptor partial agonists.

25 6. A compound according to claim 2 selected from the group consisting of  
(*R/S*)-6,7,7a,11-tetrahydro-7a-methyl-4-trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-  
a]quinoline; (*R/S*)-3-fluoro-6,7,7a,11-tetrahydro-7a-methyl-4-trifluoromethyl-2-  
pyridono[5,6-g]pyrrolidino[1,2-a]quinoline; (*R/S*)-6,7,7a,11-tetrahydro-1,7a-dimethyl-4-  
30 trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-a]quinoline; (*R/S*)-3-fluoro-6,7,7a,11-

- tetrahydro-1,7a-dimethyl-4-trifluoromethyl-2-pyridono[5,6-g]pyrrolidino[1,2-a]quinoline; 11-(trifluoromethyl)-9-pyridon[6,5-i]julolidine; 8-methyl-11-(trifluoromethyl)-9-pyridon[6,5-i]julolidine; 7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 6-Difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-2,2,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 6-difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-2,2,9-trimethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-1,2,2,9-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 6-difluoromethyl-7-fluoro-1,2,3,4-tetrahydro-1,2,2,9-tetramethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2-dihydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-2,2,4-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 1,10-[1,3-dihydro-3-oxo-(2,1-isoxazolyl)]-1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2-dihydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-2,2,4,10-tetramethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-2,2,4,9,10-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 7-fluoro-1,2,3,4-tetrahydro-1,2,2,4,10-pentamethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 1,2,3,4-tetrahydro-1-hydroxy-2,2-dimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 1,2,3,4-tetrahydro-1-hydroxy-2,2,9-trimethyl-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; 2,2-diethyl-7-fluoro-1,2,3,4-tetrahydro-6-trifluoromethyl-8-pyridono[5,6-g]quinoline; (R/S)-4-Ethyl-1-formyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; (R/S)-4-Ethyl-1,2,3,4-tetrahydro-1-(trifluoroacetyl)-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; (R/S)-1-Acetyl-4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; (R/S)-4-Ethyl-1,2,3,4-tetrahydro-10-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; 1,2,3,4-Tetrahydro-2,2-dimethyl-10-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; 1,2,3,4-Tetrahydro-2,2-dimethyl-7,10-dinitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline; and (R/S)-4-Ethyl-1,2,3,4-tetrahydro-1-nitro-6-(trifluoromethyl)-8-pyridono[5,6-g]quinoline quinoline.

7. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition according to claim 7, wherein the composition is formulated for oral, topical, intravenous, suppository or parental administration.

5 9. A pharmaceutical composition according to claim 7, wherein the compound is administered to a patient as a dosage unit at from about 1 $\mu$ g/kg of body weight to about 500 mg/kg of body weight.

10. A pharmaceutical composition according to claim 7, wherein the compound is administered to a patient as a dosage unit at from about 10 $\mu$ g/kg of body weight to about 250 mg/kg of body weight.

11. A pharmaceutical composition according to claim 7, wherein the compound is administered to a patient as a dosage unit at from about 20 $\mu$ g/kg of body weight to about 100 mg/kg of body weight.

12. A pharmaceutical composition according to claim 7, wherein the composition is effective in treating and/or modulating acne, male-pattern baldness, male hormone replacement therapy, wasting diseases, hirsutism, stimulation of hematopoiesis, hypogonadism, prostatic hyperplasia, hormone-dependent cancers such as prostate and breast cancer, and as anabolic agents.

13. A method of affecting androgen receptor activity comprising the *in vivo* administration of a compound according to claim 1.

25

14. A method of affecting androgen receptor activity comprising the *in vivo* administration of a composition according to claim 7.

15. A method of modulating a process mediated by androgen receptors comprising administering to a patient an effective amount of a compound according to claim 1.
- 5 16. A method of modulating a process mediated by androgen receptors comprising administering to a patient an effective amount of a composition according to claim 7.
- 
- 10 17. A method of modulating a process mediated by androgen receptors comprising administering to a patient an effective amount of a compound according to claim 1.
- 15 18. A method of treating a patient according to claim 17, wherein the compound is effective in treating and/or modulating modulating acne, male-pattern baldness, male hormone replacement therapy, wasting diseases, hirsutism, stimulation of hematopoiesis, hypogonadism, prostatic hyperplasia, hormone-dependent cancers such as prostate and breast cancer, and as anabolic agents.
- 20 19. A method of treating a patient requiring androgen receptor therapy comprising administering to said patient and effective amount of a compound according to claim 1.
- 25 20. A method of treating a patient according to claim 19, wherein the composition is effective in treating and/or modulating acne, male-pattern baldness, male hormone replacement therapy, wasting diseases, hirsutism, stimulation of hematopoiesis, hypogonadism, prostatic hyperplasia, hormone-dependent cancers such as prostate and breast cancer, and as anabolic agents.

# INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 97/11222

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D487/04 C07D491/06 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 11215 A (LIGAND PHARMACEUTICALS ) 27 April 1995 see claims; examples ---	1-20
A	WO 91 00732 A (ENDORECHERCHE INC.) 24 January 1991 see claims; examples ---	1-20
A	A. M. NADZAN ET. AL.: "Nybomycin. 8. Biosynthetic Origin of the Central Ring Carbons Studied by 13C-Labeled Substrates." JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 98, no. 16, 4 August 1976, WASHINGTON DC, US, pages 5012-4, XP002043526 see whole document --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

14 October 1997

Date of mailing of the international search report

19. 11. 97

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3018

Authorized officer

Helps, I

## INTERNATIONAL SEARCH REPORT

Inter. J. Appl. Application No

PCT/US 97/11222

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 19458 A (LIGAND PHARMACEUTICALS) 27 June 1996 cited in the application see claims; examples 138-169 -----	1-20

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/US 97/11222

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9511215 A	27-04-95	AU 8081894 A	08-05-95
WO 9100732 A	24-01-91	AU 2559897 A	04-09-97
		AU 5856090 A	06-02-91
		AU 6748194 A	08-09-94
		CA 2063378 A	08-01-91
		EP 0485392 A	20-05-92
		GR 1001164 B	24-05-93
		JP 4506797 T	26-11-92
WO 9619458 A	27-06-96	AU 4597796 A	10-07-96
		NO 972591 A	14-08-97